

# Neoplasms in Neurofibromatosis 1 Are Related to Gender But Not to Family History of Cancer

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The risk of malignancies among persons with neurofibromatosis 1 (NF1) is higher than in the general population, but the excess risk has not been precisely estimated. The effects of gender and inheritance pattern on cancer risk are unclear. Therefore, we conducted a historical cohort study to determine cancer risk factors by contacting 138 Caucasian NF1 patients originally seen at Baylor College of Medicine (BCM) in Houston between 1978 and 1984. A total of 304 patients of all ethnic groups were evaluated at BCM during this period. We successfully located 173 patients, 138 of who were Caucasian. We computed standardized

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incidence ratios (SIRs) with the age-, gender-, and time period-specific rates from the Connecticut Tumor Registry for 2,094 person-years of observation (median follow-up = 16 years). Eleven incident tumors were reported. Females were at much higher risk of cancer than males (SIR = 5.6, 95% confidence interval (CI) 2.7–10.3 and SIR = 0.6; 95% CI, 0.0–3.0, respectively). We found no elevated cancer risk in unaffected first-degree relatives, regardless of whether the proband had cancer or not (SIR = 1.1 95% CI, 0.6–1.8 and SIR = 1.0, 95% CI, 0.6–1.5, respectively). Our results suggest that malignancy in the proband is not the result of a modifying gene that has a significant impact on general cancer risk. *Genet. Epidemiol.* 20:75–86, 2001. © 2001 Wiley-Liss, Inc.

**Key words:** family studies; cohort studies; gender; risk

## INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder that occurs in approximately 1 in 3,500 live births [Samuelsson and Axelsson, 1981] and was first defined by Friedreich von Recklinghausen in 1882 [Crowe et al., 1956]. The NF1 genotype is nearly 100% penetrant, but there is considerable heterogeneity in clinical expression. Malignancies such as optic pathway gliomas [Lewis et al., 1984; Listerneck et al., 1989], and malignant peripheral nerve sheath tumors (MPNSTs) [Matsui et al., 1993] occur frequently in patients with NF1. However, reports of factors that increase cancer risk in individuals with NF1 conflict [Riccardi et al., 1983; Lewis et al., 1984; Sorenson et al., 1986; Schneider et al., 1986; Huson et al., 1989; Szudek et al., 1997; Zvulunov et al., 1998]. For example, females with NF1 were reported to have a higher risk of tumors than males in one study [Sorenson et al., 1986] but not in others [Lewis et al., 1984; Schneider et al., 1986; Huson et al., 1989; Zvulunov et al., 1998]. Likewise, inheriting the NF1 gene from an affected parent (compared to a new mutation) increased malignancy risk in some studies [Schneider et al., 1986; Zvulunov et al., 1998] but not others [Lewis et al., 1984; Huson et al., 1989].

The variable expressivity of NF1, even among members of the same family who presumably have the same mutation, suggests the presence of modifier genes. Easton and colleagues [1993] reported a high correlation of five phenotypic features, such as number of café-au-lait spots among monozygotic twins but low correlations among more distant relatives. This observation implied that the NF1 mutation plays a minor role in phenotypic variability; Easton and co-workers concluded that the NF1 phenotype is probably determined by the genotype at other modifying loci [Easton et al., 1993].

Therefore, our study had two objectives. The first was to determine whether gender influences cancer risk in NF1 patients and whether inheriting a mutant allele increases the risk of developing cancer compared with acquiring a new mutation. The second objective was to evaluate the role of family cancer history in determining the cancer phenotype in NF1, that is, to determine whether the occurrence of malignancies in first-degree relatives who are unaffected with NF1 might modify the risk of cancer in the NF1 affected probands. We compared the observed number of cancers in unaffected and affected relatives of NF1 patients to the number expected based on cancer rates from the Connecticut Tumor Registry. An affected family mem-

ber is a first-degree relative with NF1. If familial cancers do not modify risk in the proband, then the ratio of observed to expected number of cancers (standardized incidence ratio [SIR]) should be close to 1.0 among unaffected first-degree relatives of NF1 probands regardless of the cancer status of the proband. This model assumes that the putative modifier loci would influence the general cancer risk in first-degree relatives who are unaffected with NF1. We tested these hypotheses by conducting a long-term follow-up study of families with NF1 who had been seen from 1978 to 1984 in the Neurofibromatosis Clinic at Baylor College of Medicine (BCM) in Houston, Texas.

## SUBJECTS AND METHODS

A list of all NF1 patients seen at the BCM Neurofibromatosis Clinic was compiled for the years 1978 through 1984. Although the NF Clinic continued after 1984, we chose that year to maximize the duration of follow-up. We used the standard diagnostic criteria for NF1 for study inclusion, that is, the presence of two or more of the following clinical criteria: six or more café-au-lait spots ( $\geq 5$  mm in diameter in pre-pubescent subjects or  $\geq 15$  mm in post-pubescent subjects), axillary or inguinal freckling; two or more iris Lisch nodules; two or more neurofibromas of any type or at least one plexiform neurofibroma; distinctive tumor of the anterior optic pathway (e.g., optic nerve glioma); distinctive osseous lesions (e.g., sphenoid bone dysplasia); or a first-degree relative diagnosed with NF1 by these criteria [NIH Consensus Development Conference, 1988].

Patients and their families were located as part of an ongoing long-term study of NF1 conducted at BCM in collaboration with The University of Texas M.D. Anderson Cancer Center (M.D. Anderson). Because we used comparative gender-, age-, and calendar year-specific rates from the Connecticut Tumor Registry (CTR, which provides rates for Caucasians), we restricted this analysis to Caucasian NF1 families and one family in which the proband was of mixed Caucasian/American Indian ancestry and had Caucasian first-degree relatives. When several members of the same NF1 family were seen at BCM, we defined a proband as either the first affected member of a family who was evaluated at the Neurofibromatosis Clinic or the eldest, when multiple family members were seen on the same day. We defined a new mutation case as the first member of a kindred diagnosed with NF1 who had unequivocally unaffected parents.

The project was approved by the Institutional Review Boards for Human Subject Research of both BCM and M.D. Anderson. The study families were traced and located between July 1997 and April 1998. To locate the probands, we used the next-of-kin names and telephone numbers from medical records, directory assistance in cities of the last known residence for patients or family members, and Internet resources, including Switchboard, Four11, and Public Data, to search Texas drivers' license rolls. Trained interviewers contacted and invited each subject or available next-of-kin located to participate in the study. Verbal consent was obtained by telephone before interviews were conducted; each subject could refuse to (continue to) participate at any time. An extensive individual-health and family-health questionnaire was administered to each person to solicit information on the presence or absence of NF1 and cancer in both the study subjects and their first-degree relatives,

and the dates of birth, death, and cancer and NF1 diagnoses. The cancers reported in probands or family members were not confirmed independently by other means, such as examining medical records or death certificates [Love et al., 1985; Bondy et al., 1994; Airewele et al., 1998].

We used general population cancer rates from the CTR as an external comparison. The CTR was selected because it is the only population-based registry that contains rates from 1935, and some of our study subjects began accruing person-time in the 1930s. The Standardized Incidence Ratios (SIRs) were calculated with the Cohort Analysis for Genetic Epidemiology (CAGE) computer program [Lustbader and McLaughlin, 1995], which applied the CTR age-, gender-, and time period-specific rates to the person-years experienced by the study cohort. For the calculations, each person was allowed to contribute one cancer in the follow-up period because the CAGE program utilizes first primary cancers from the CTR to compute the expected number of cancer. All invasive malignancies and all brain tumors (benign or malignant) were considered cancer events. We excluded carcinoma in situ and non-melanoma skin cancers. For probands, the person-time at risk was calculated from the date of the initial visit to the BCM Neurofibromatosis Clinic to the date of death, cancer diagnosis, or interview, whichever came first. Cancers present at the first BCM visit and those cancers diagnosed within 6 months were also excluded. For unaffected siblings and offspring, person-years were calculated from the date of birth to the same endpoint as the proband. For the proband's parents (because they had to survive to reproductive age), we began accruing person-time from the date of birth of the proband either to their own diagnosis with cancer, to their date of death, or to the date of interview, whichever came first.

The observed to expected (O/E) numbers of cancers were compared by gender and by whether the neurofibromatosis was inherited or a new mutation. We also partitioned the data for unaffected first-degree relatives by whether or not the proband had any cancer. This comparison of observed to expected SIRs was assumed to follow a Poisson distribution for the calculation of 95% confidence intervals (CIs), and all tests for statistical significance were two sided. We calculated the chi-square test for heterogeneity to detect significant differences in the comparison of SIRs by subgroups (such as males vs. females) [Breslow and Day, 1987]. We calculated separate SIRs for the probands, the affected first-degree relatives who were also seen at BCM, and for both groups combined. Because optic pathway gliomas are part of the diagnostic criteria for NF1, we computed SIRs with and without the inclusion of incident anterior optic pathway tumors.

## RESULTS

A total of 304 patients with NF1 were evaluated at BCM between 1978 and 1984 (Fig. 1). One hundred and seventy-three of the 304 patients (57%) in 124 families were located and then interviewed for this study. After restriction to Caucasian families ( $n = 102$ ) and one family of mixed Caucasian/American Indian ancestry, 103 families (83%) remained for analysis. These 103 families included 371 first-degree relatives unaffected with NF1. Of the 195 individuals who had NF1, 138 had been evaluated at BCM; 57 first-degree relatives were never seen at BCM.

The demographic characteristics of the affected individuals who were evaluated

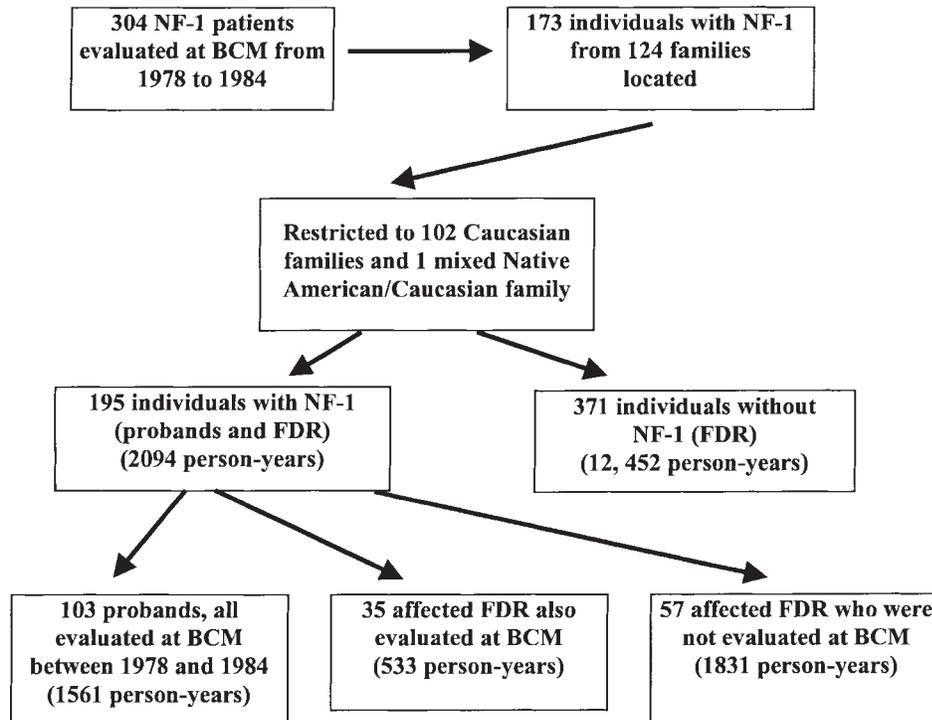


Fig. 1. Flow chart showing the numbers of affected individuals and their first-degree relatives (FDR).

at BCM are shown in Table I. The median age at time of presentation for probands was 19 years. In the BCM cohort, 54% of the 138 individuals presented with new NF1 mutations. Males and females made up 46 and 54% of the BCM cohort, respectively. During the follow-up period, nine cancers (three optic pathway tumors and one each of brain, breast, small intestine, multiple myeloma, pancreas, and bone) were diagnosed in eight probands. The proband diagnosed with cancer of the small intestine subsequently developed multiple myeloma. Three cancers (brain, MPNST, and female breast) occurred during the observation period in the group of 35 NF1 affected first-degree relatives also seen at BCM. In all, three patients reportedly had brain tumors, and all three had had a prior optic pathway tumor. Of the eight individuals with both cancer and inherited NF1, six inherited NF1 from their fathers. The difference was not statistically significant (Fisher's exact  $P$  value = 0.13).

In addition to the cancers diagnosed during our follow-up period, 18 reported cancers (14 optic pathway gliomas and one each of brain, pancreas, lung, and MPNST) occurred in probands and affected first-degree relatives before or within 6 months of presentation at BCM; these tumors were not included in the SIR analysis because they were considered prevalent events. Of these 18 cancers identified at presentation or within 6 months, 10 were in females and 14 occurred in subjects with new mutations. The difference in proportion of excluded prevalent cancers between individuals with new mutations compared to individuals who had inherited NF1 approached statistical significance ( $\chi^2 = 3.73$ ,  $P = 0.05$ ). The difference in the proportion of ex-

**TABLE I. Demographic Characteristics of Individuals With NF1 Evaluated at BCM Between 1978 and 1984**

	Probands (N = 103)		First-degree relatives with NF1 (N = 35)		Entire BCM cohort (N = 138)	
	Number	(%)	Number	(%)	Number	(%)
Age at presentation						
0–4	24	(23.3)	5	(14.3)	29	(21.0)
5–9	15	(14.6)	9	(25.7)	24	(17.4)
10–19	13	(12.6)	13	(37.1)	26	(18.8)
20–29	15	(14.6)	2	(5.7)	17	(12.3)
30–39	17	(16.5)	6	(17.2)	23	(16.7)
>39	19	(18.4)	0	(0.0)	19	(13.8)
Inheritance pattern of NF1						
New mutation	75	(72.8)	0	(0.0)	75	(54.3)
Inherited	23	(22.3)	34	(97.1)	57	(41.3)
Unknown	5	(4.9)	1	(2.9)	6	(4.4)
Gender						
Male	46	(44.6)	18	(51.4)	64	(46.4)
Female	57	(55.3)	17	(48.6)	74	(53.6)
Ethnicity						
Caucasian	102	(99.0)	35	(100.0)	137	(99.3)
Mixed Caucasian and Native American	1	(1.0)	0	(0.0)	1	(0.7)

cluded prevalent cancers between males and females was not statistically significant ( $\chi^2 = 0.06$ ,  $P = 0.81$ ).

The SIRs for all the probands and their first-degree relatives evaluated at BCM are shown as Table II. The SIR for all cancers among the probands was 2.5 (O/E = 8/3.3, 95% CI: 1.1–4.8). The SIR was 4.7 for persons who inherited NF1 and 1.4 for those with a new mutation; this difference in SIRs approaches statistical significance ( $\chi^2 = 3.09$ ,  $P = 0.08$ ). The SIR for cancer was 0.6 in males compared with 4.52 in females. The chi-square test for heterogeneity showed a significant difference in the SIRs between males and females ( $\chi^2 = 5.12$ ,  $P = 0.02$ ). For the first-degree relatives with NF1 who were also seen at BCM (N = 35), the overall SIR for cancer was 8.3 (95% CI: 1.7–24.3). When all the individuals evaluated at BCM were combined (i.e., including 35 first-degree relatives), the SIRs were similar to those for the probands alone. The overall SIR for cancer for this BCM cohort was 3.0 (95% CI, 1.5–5.4). The risk of malignancy was significantly higher among those who inherited NF1 from a parent (SIR = 5.7, 95% CI, 2.5–11.2) as compared to those with new mutations (SIR = 1.4, 95% CI, 0.3–4.1), respectively ( $\chi^2 = 5.05$ ,  $P = 0.03$ ). A significant difference in SIRs was observed between males and females of 0.6 (95% CI, 0.0–3.0) and 5.6 (95% CI, 2.7–10.3), respectively ( $\chi^2 = 7.67$ ,  $P = 0.006$ ). When the three optic pathway gliomas (all occurred in probands) were excluded from the calculations of incident tumors, the SIR for malignancy among the BCM cohort (N = 138) was 2.2 (95% CI, 1.0–4.3). The difference in SIRs observed between males and females; and between new mutation and inherited NF1 persisted ( $\chi^2 = 4.67$ ,  $P = 0.03$  and  $\chi^2 = 4.19$ ,  $P = 0.04$ , respectively).

**TABLE II. SIRs of Individuals With NF1 Evaluated at BCM Between 1978 and 1984 With Optic Pathway Gliomas Included and Not Included as Tumors Occurring in the Follow-Up Period**

	Optic pathway gliomas included						Optic pathway gliomas excluded				
	Number	Person- years	Cancers observed	Cancers expected	SIR	95% CI	Person- years	Cancers observed	Cancers expected	SIR	95% CI
Probands	103	1,561	8	3.26	2.5	1.1–4.8	1,582	5	3.27	1.5	0.5–3.6
Inherited NF1	23	334	5	1.07	4.7	1.5–10.9	348	3	1.07	2.8	0.6–8.2
New mutation	75	1,143	3	2.15	1.4	0.3–4.1	1,150	2	2.15	0.9	0.1–3.4
Unknown	5	84	0	0.04	—	—	84	0	0.04	—	—
Males	46	705	1	1.71	0.6	0.0–3.3	705	1	1.71	0.6	0.0–3.3
Females	57	856	7	1.55	4.5	1.8–9.3	877	4	1.55	2.6	0.7–6.6
First-degree relatives with NF1	35	533	3	0.36	8.3	1.7–24.3	533	3	0.36	8.3	1.7–24.3
Inherited NF1	34	515	3	0.34	8.8	1.8–25.8	515	3	0.34	8.8	1.8–25.8
New NF1 mutation	0	0	0	0	—	—	0	0	0.00	—	—
Unknown	1	18	0	0.02	—	—	18	0	0.02	—	—
Males	18	275	0	0.12	—	—	275	0	0.12	—	—
Females	17	258	3	0.23	13.0	2.7–38.1	258	3	0.23	13.0	2.7–38.1
All Individuals with NF1	138	2,094	11	3.62	3.0	1.5–5.4	2,115	8	3.63	2.2	1.0–4.3
Inherited NF1	57	849	8	1.41	5.7	2.5–11.2	863	6	1.41	4.3	1.6–9.3
New mutation	75	1,143	3	2.15	1.4	0.3–4.1	1,150	2	2.15	0.9	0.1–3.4
Unknown	6	102	0	0.06	—	—	102	0	0.06	—	—
Males	64	980	1	1.85	0.6	0.0–3.0	980	1	1.83	0.6	0.0–3.0
Females	74	1,114	10	1.79	5.6	2.7–10.3	1,135	7	1.78	3.9	1.6–8.1

—, no cases.

The SIRs for unaffected first-degree relatives are shown as Table III. Among the 371 affected first-degree relatives, the O/E numbers of cancer cases were the same (32/32). No significantly elevated risk of cancer was observed in siblings, fathers, or mothers; we could not evaluate offspring because none of them had cancer. The risks for cancers of the breast in women, prostate, digestive tract, brain, and lung cancer did not differ significantly from those for the general population (i.e., 95% CIs for site specific SIRs did not exclude the null value of 1.0 [data not shown]). When the unaffected first-degree relatives were partitioned by the history of cancer in the proband, no significant differences in the SIRs were observed (1.1, 95% CI, 0.6–1.8; vs. 1.0, 95% CI, 0.6–1.5. There was also no difference in the SIRs observed for unaffected first-degree relatives of probands with inherited NF1, compared to the relatives of probands whose NF1 was due to a new mutation.

## DISCUSSION

Several studies have found that individuals with NF1 have a higher risk of malignant tumors (particularly brain and peripheral nerves) than does the general population [Sorenson et al., 1986; Matsui et al., 1993, Zoller et al., 1997]. In this study, we found that the SIR for cancer in a cohort of NF1 probands was more than double that of the comparative population. Our results are a conservative estimate, as we excluded a number of cancers that were diagnosed by routine screening at the time of presentation to the BCM Clinic. In a 40-year follow-up study of neurofibromatosis conducted in Denmark, NF1 probands had a relative risk of 4.0 (95% CI 2.8–5.6) for malignancies, with a preponderance of gliomas [Sorenson et al., 1986]. As expected, we also found a high proportion of brain tumors (including anterior optic pathway gliomas).

In our study, females with NF1 who were evaluated at BCM had a significantly higher SIR for cancer than did affected males. Similarly, a Danish study [Sorenson

**TABLE III. SIRs in First-Degree Relatives Without NF1\***

	Number	Cancers observed	Cancers expected	SIR	95% CI
All	371	32	32.00	1.0	0.7–1.4
Siblings	154	5	8.58	0.6	0.2–1.4
Fathers	87	11	12.18	0.9	0.5–1.6
Mothers	84	16	10.78	1.5	1.0–2.4
Offspring	46	0	0.45	—	—
Males	195	13	16.84	0.8	0.4–1.3
Females	176	19	15.16	1.3	0.8–2.0
New NF1 mutation in proband	310	28	26.53	1.1	0.7–1.5
Inherited NF1 in proband	59	4	5.47	0.7	0.2–1.9
Proband with cancer	114	14	13.22	1.1	0.6–1.8
Proband without cancer	257	18	18.78	1.0	0.6–1.5
Proband with cancer excluding OPT	41	4	7.60	0.5	0.1–1.4
Proband with cancer including OPT	330	28	24.40	1.2	0.8–1.7

\*OPT, optic pathway tumors.

et al., 1986] found a significant twofold elevated relative risk for cancer among affected females (proband and relatives), but other reports did not [Schneider et al., 1986; Huson et al., 1989; Zvulunov et al., 1998]. Also, an increased risk of malignancy in females has been reported in other autosomal dominant diseases, such as neurofibromatosis type 2, in which females have an increased incidence of meningiomas [Evans et al., 1995]. Female hormones may affect meningioma growth, as these tumors have estrogen and progesterone receptors [Martuza et al., 1985; Roelvinck et al., 1987]. Although steroid receptors have been found in tumors originating from the nerve sheath, including soft tissue sarcomas [Chaudhuri et al., 1981, 1982], the increased incidence of cancer (other than central nervous system tumors) in this NF1 cohort did not involve any specific type or tissue. The role of gender in risk of incident tumors remains unclear and requires further elucidation with prospective studies.

Most studies reported that 50% of the NF1 cases are inherited [Borberg, 1951; Crowe et al., 1956]. When we combined all the affected individuals who were evaluated in BCM, the ratio of sporadic to inherited NF1 (1.3 to 1) was consistent with previous reports. Among the 138 NF1 patients seen at BCM, persons with inherited NF1 had a significantly higher SIR for cancer than did persons with new mutations. The reason for this difference is unknown. The likely explanation for the result in the present study is the excess of prevalent cancers that were excluded among individuals whose NF1 was due to a new mutation compared to individuals with inherited NF1. However, our result is consistent with the results of some published studies [Schneider et al., 1986; Zvulunov et al., 1998]. In another report, new mutations conferred elevated cancer risk, particularly in subjects under age 18 years [Huson et al., 1989]. However, the authors discounted this finding as the result of ascertainment bias [Huson et al., 1989]. It is unlikely that somatic mosaicism among individuals with sporadic NF1 played a major role, because 48% of the offspring of sporadic NF1 individuals in the present study also had NF1 (data not shown). If a substantial proportion of the new mutation patients were mosaic, we would have expected a lower percentage of affected offspring as has been shown in NF-2 [Kluwe and Mautner, 1998]. An alternate explanation for the difference in cancer rates between inherited and new mutation cases is genetic anticipation. Although the molecular basis of genetic anticipation in cancer families is not understood, it has been reported for familial leukemia, neuroblastoma, and Hodgkin's disease [Horwitz et al., 1996; Plon, 1997; Shugart, 1998].

In our study, of the eight individuals with both inherited NF1 and cancer, six inherited NF1 from their fathers. Although this finding was not statistically significant possibly due to small sample size, it is possible that the parent from whom a NF1 mutation was inherited may influence the risk of cancer and thus might suggest a role for genetic imprinting. This same phenomenon has been observed in the occurrence of pancreatic cancer in families with familial pancreatitis [Lowenfels et al., 1997].

To our knowledge, ours is the first study to address the risk of cancer among unaffected relatives of NF1 patients. We did not observe an increased cancer risk in unaffected relatives. Furthermore, the risks for cancers of the breast in women, prostate, digestive tract, brain, and lung did not differ significantly from those for the general population (95% CIs for site-specific SIRs did not exclude the null value of 1.0 [data not shown]). When the families were partitioned by the history of invasive cancer in the proband, no significant differences in the SIRs were observed. This

result among unaffected first-degree relatives of NF1 patients does not support the existence of a modifying gene or genes that has a significant impact on general cancer risk. The results from this study do not reject the existence of specific modifier genes that influence the risk of cancer in individuals who carry an NF1 mutation, since we did not design our study to evaluate that possibility.

Lack of documentation of reported cancers could have caused differential misclassification of outcome in this study. It is impossible, however, to predict the direction or the magnitude of such misclassification. Previous studies have documented the accuracy of cancer reports in first-degree relatives, at least for the major cancer sites of breast, brain, lung, colon, prostate, and pancreas [Love et al., 1985; Bondy et al., 1994; Airewele et al., 1998]. These studies have also reported that the least accurate reports are for metastatic cancer and cancer involving the female genital tract [Airewele et al., 1998]. Although we did not independently confirm cancers reported in NF1 family members, only 19% of these cancers were of potentially metastatic sites or from the female genital tract (data not shown).

We successfully located 173 of the 304 patients (57%) evaluated at the BCM clinic between 1978 and 1984. Bias would be present only if those who were not located had a different cancer experience than those who were located. If patients were not found because they had died from cancer, then the SIR would be biased downward. The contrary argument (i.e., that individuals who developed cancer were more likely to be located and thus the SIRs would be biased upward) may also be valid because these individuals would probably have visited hospitals or health care facilities repeatedly (particularly Baylor Affiliated Hospitals and M.D. Anderson Cancer Center). It is not possible to predict the direction of bias that may have occurred in this study, but to attempt to evaluate it, we compared the available characteristics from baseline descriptors of individuals located with those who were not found in a subset of our study population (i.e., probands evaluated between 1978 and 1983). We found no significant differences between these two groups by the year of first BCM clinic visit, gender, race, new versus inherited mutation, or disease severity at first BCM clinic visit (data not shown).

In summary, our results do not support the existence of a modifying gene that has a significant impact on general cancer risk in NF1. We confirmed that individuals affected by NF1 had a higher cancer risk than did the general population. We also found that both females with NF1 and those who inherited NF1 had higher cancer risks than males or than those with new mutations, respectively. Additional investigations may detect differences in the nature of inherited and new mutations or between gender that explain the difference in cancer risks between these paired groups. Because of the small sample size (103 probands and 371 unaffected relatives), we were unable to partition the first-degree relatives by specific cancer sites in the proband or by age of cancer onset. Future research on NF1 cancer phenotype should evaluate risk by cancer site and by age of onset of cancer.

## ELECTRONIC-DATABASE INFORMATION

The URLs for locating resources in this article are as follows:

Switchboard, <http://www.switchboard.com>; Four11, <http://www.four11.com>; Public Data, <http://www.publicdata.com>

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## REFERENCES

- Airewele G, Adatto P, Cunningham J, Mastromarino C, Spencer C, Sharp M, Sigurdson A, Bondy M. 1998. Family history of cancer in patients with glioma: a validation study of accuracy. *J Nat Cancer Inst* 90:543–4.
- Bondy ML, Strom SS, Colopy MW, Brown BW, Strong LC. 1994. Accuracy of family history of cancer obtained through interviews with relatives of patients with childhood sarcoma. *J Clin Epidemiol* 47:89–96.
- Borberg A. 1951. Clinical and genetic investigations into tuberous sclerosis and von Recklinghausen's neurofibromatosis. *Acta Psychiatr Neurol Scand (Suppl II)*:1–239.
- Breslow NE, Day NE. 1987. The design and analysis of cohort studies. *IARC Sci Publ* 82:65–72, 91–118.
- Chaudhuri PK, Walker MJ, Beattie CW, Das Gupta TK. 1981. Distribution of steroid hormone receptors in human soft tissue sarcomas. *Surgery* 90:149–53.
- Chaudhuri PK, Walker WJ, Das Gupta TK, Beattie CW. 1982. Steroid receptors in tumors of nerve sheath origin. *J Surg Oncol* 20:205–6.
- Crowe FW, Schull WJ, Neel JV. 1956. A clinical, pathological and genetic study of multiple neurofibromatosis. Springfield, IL: Charles C. Thomas.
- Easton DF, Ponder MA, Huson SM, Ponder BA. 1993. An analysis of variation in expression of neurofibromatosis (NF) type 1 (NF-1): evidence for modifying genes. *Am J Hum Genet* 53:305–13.
- Evans DGR, Blai V, Strachan T, Lye RH, Ramsden RT. 1995. Variation of expression of the gene for type 2 neurofibromatosis: absence of a gender effect on vestibular schwannomas, but confirmation of a preponderance of meningiomas in females. *J Laryngol Otol* 109:830–5.
- Horwitz M, Goode EL, Jarvik GP. 1996. Anticipation in familial leukemia. *Am J Hum Genet* 59:990–8.
- Huson SM, Compston DAS, Clark P, Harper PS. 1989. A genetic study of von Recklinghausen neurofibromatosis in south east Wales. Prevalence, fitness, mutation rate, and effect of parental transmission on severity. *J Med Genet* 26:704–11.
- Kluwe L, Mautner VF. 1998. Mosaicism in sporadic neurofibromatosis 2 patients. *Hum Mol Genet* 7:2051–5.
- Lewis RA, Gerson LP, Axelson KA, Riccardi VM, Whitford R. 1984. von Recklinghausen neurofibromatosis: incidence of optic gliomata. *Ophthalmology* 91:929–35.
- Listernick R, Charrow J, Greenwald MJ, Esterly NB. 1989. Optic gliomas in children with neurofibromatosis type 1. *J Pediatr* 114:788–92.
- Love RR, Evans AM, Josten DM. 1985. The accuracy of patient reports of a family history of cancer. *J Chron Dis* 38:289–93.
- Lowenfels AB, Maisonneuve P, DiMagno EP, Elitsur Y, Gates LK Jr, Perrault J, Whitcomb DC. 1997. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. *J Natl Cancer Inst* 89:442–6.
- Lustbader ED, McLaughlin PR. 1995. CAGE: cohort analysis for genetic epidemiology. Philadelphia, PA: Fox Chase Cancer Center.

- Martuza RL, Miller DC, MacLaughlin DT. 1985. Estrogen and progestin binding by cytosolic and nuclear fractions of human meningiomas. *J Neurosurg* 62:750-6.
- Matsui I, Tanimura M, Kobayashi N, Sawada T, Nagahara N, Akatsuka J. 1993. Neurofibromatosis Type 1 and childhood cancer. *Cancer* 72:2746-53.
- National Institutes of Health Consensus Development Conference. 1988. Neurofibromatosis conference statement. *Arch Neurol* 45:575-8.
- Plon SE. 1997. Anticipation in pediatric malignancies *Am J Hum Genet* 60:1256-7.
- Riccardi VM, Riccardi SL, Norton HJ, Martin MC, Eichner J. 1983. Likelihood of severe disease among von Recklinghausen neurofibromatosis patients. *Am J Hum Genet* 35:114A.
- Roelvinck NC, Kamphorst W, van Alphen HA, Rao BR. 1987. Pregnancy-related brain and spinal tumors. *Arch Neurol* 44:209-15.
- Samuelsson B, Axelsson R. 1981. Neurofibromatosis: a clinical and genetic study of 96 cases in Gothenburg, Sweden. *Acta Derm Venereol Suppl (Stockh)* 95:67-71.
- Schneider M, Obringer AC, Zackai E, Meadows AT. 1986. Childhood neurofibromatosis: risk factors for malignant disease. *Cancer Genet Cytogenet* 21:347-54.
- Shugart YY. 1998. Anticipation in familial Hodgkin lymphoma. *Am J Hum Genet* 63:270-2.
- Sorensen SA, Mulvihill JJ, Nielsen A. 1986. Long-term follow-up of von Recklinghausen neurofibromatosis: Survival and malignant neoplasms. *N Engl J Med* 314:1010-5.
- Szudek J, Riccardi VM, Friedman JM. 1997. Associations of clinical features in children with neurofibromatosis type 1 (NF-1). *Am J Hum Genet* 61:A179.
- Zoller ME, Rembeck B, Oden A, Samuelsson M, Angervall L. 1997. Malignant and benign tumors in patients with neurofibromatosis type 1 in a defined Swedish population. *Cancer* 79:2125-35.
- Zvulunov A, Weitz R, Metzker A. 1998. Neurofibromatosis type 1 in childhood: evaluation of clinical and epidemiologic features as predictive factors for severity. *Clin Pediatr* 37:295-300.