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Distinctive Cancer Associations in Patients With Neurofibromatosis Type 1

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Abstract

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Purpose

The current study was designed to determine the risk of cancer in patients with neurofibromatosis type 1 (NF1) by cancer type, age, and sex with unprecedented accuracy to be achieved by combining two total population–based registers.

Patients and Methods

A population-based series of patients with NF1 (N = 1,404; 19,076 person-years) was linked to incident cancers recorded in the Finnish Cancer Registry and deaths recorded in the national Population Register Centre between 1987 and 2012. Standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs) were calculated for selected cancer types. Survival of the patients with cancer with and without NF1 was compared.

Results

In malignant peripheral nerve sheath tumors and CNS tumors, the cancers traditionally associated with NF1, we observed SIRs of 2,056 (95% CI, 1,561 to 2,658), and 37.5 (95% CI, 30.2 to 46.0), respectively, and SMRs of 2,301 (95% CI, 1,652 to 3,122) and 30.2 (95% CI, 19.1 to 45.2), respectively. We found an unequivocally increased risk for breast cancer. In particular, SIR was 11.1 (95% CI, 5.56 to 19.5) for breast cancer in women

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with NF1 age < 40 years; the overall SMR for breast cancer was 5.20 (95% CI, 2.38 to 9.88). Particularly high overall SIRs were observed in patients with NF1 age < 15 years: women, 87.6 (95% CI, 58.6 to 125); men, 45.6 (95% CI, 28.4 to 68.5). An estimated lifetime cancer risk for patients with NF1 was 59.6%. The 5-year survival of patients with cancer and NF1, excluding nervous tissue cancers, was worse than that of comparable patients with cancers without NF1 (54.0% *v* 67.5%; *P* = .01).

Conclusion

Our results emphasize the general cancer proclivity of patients with NF1. These findings should translate to clinical practices to determine clinical interventions and focused follow-up of patients with NF1.

INTRODUCTION

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Neurofibromatosis type 1 ([NF1](#); Online Mendelian Inheritance in Man, 162200), an autosomal-dominant tumor predisposition syndrome¹ with a birth rate as high as one in 2,000,² is caused by mutations of the *NF1* gene on chromosome 17.^{3,4} NF1 is a multisystem disease with varying combinations of benign and malignant tumors, developmental dysplasias, and functional deficits, including cognitive impairment.^{5,6} Almost all adult patients with NF1 have cutaneous neurofibromas, which are benign tumors that do not become malignant. More than one half of patients with NF1 also have plexiform neurofibromas, which may become malignant.^{7,8} The most common malignancies associated with NF1 are intracranial gliomas and [malignant peripheral nerve sheath tumors \(MPNSTs\)](#). CNS tumors occur in approximately 20% of patients with NF1 and are usually detected in early childhood.⁹ Most are low-grade pilocytic astrocytomas of the optic pathway or brainstem, but high-grade tumors also occur.⁹⁻¹¹ MPNST often arises from plexiform neurofibroma and is one of the hallmark complications of NF1. MPNST is an aggressive sarcoma with a poor survival rate. Whereas MPNST is rare in the general population, the cumulative lifetime risk for patients with NF1 is reported to be 8% to 13%.¹² In addition to malignancies originating from the nervous system, it has been suggested that other cancers, such as breast cancer, gastrointestinal stromal tumor (GIST), and pheochromocytoma, are associated with NF1.¹³⁻¹⁵ Mutations of the *NF1* gene are also frequently found in cancers of the general population, especially in melanomas, glioblastomas, and lung tumors.¹⁶

The number of epidemiologic studies on cancer incidence in patients with NF1 is limited. A Swedish study reported a relative risk of cancer of 4.0 in 70 patients with NF1.¹⁷ An analysis of a cohort of 448 patients with NF1 in the United Kingdom showed a 2.7 times higher risk of cancer compared with the general population as well as a [cumulative risk](#) of 20% by age 50 years.¹⁸ The most frequent sites of cancer were connective tissue and CNS, with [standardized incidence ratios](#) (SIRs) of 122 and 22.6, respectively.¹⁸ In another study from the United Kingdom, a relative cancer risk of 4.0 was found in a cohort presumed to have NF1.¹⁹ The most common cause of death in patients with NF1 is reported to be MPNST, which causes 26% of deaths of patients with NF1.²⁰ Duong et al²¹ reported an excess mortality rate among patients with NF1 age < 40 years, with 60% of deaths in this age group a result of MPNST.

The current study evaluates the cancer incidence and mortality in a representative population-based cohort of Finnish patients with NF1. The data document a high risk of cancer, new NF1-related cancers, and compromised cancer-related survival in NF1.

PATIENTS AND METHODS

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Patients

The study adhered to the Declaration of Helsinki principles and was approved by the Ethical Committee of the Southwest Finland Hospital District and Ministry of Social Affairs and Health of Finland. A research permit was obtained from all participating hospitals. Data for patients with NF1, described in detail by Uusitalo et al,² were ascertained from January 1, 1987, through December 31, 2011. In brief, we used codes from the International Classification of Diseases, Ninth and Tenth revisions (ICD-9 and ICD-10), to search for patients in electronic hospital registers that included all medical specialties in all secondary and tertiary medical centers in Finland. Data from the medical records of the five university hospitals and the 15 central hospitals of mainland Finland cover the entire Finnish population of 5.4 million. The diagnosis of NF1 in each patient was verified according to the National Institutes of Health clinical diagnostic criteria²² and/or mutation analysis. To avoid inclusion of false-positive cases, 535 patients were excluded on review because they did not fulfill the National Institutes of Health criteria.² After exclusion, the cohort included a total of 1,404 patients with NF1: 667 men and 737 women from 975 different pedigrees. The dates of death and emigration were obtained from the national Population Register Centre. Five patients emigrated and 217 patients died during follow-up.

Patients with NF1 were observed for cancer diagnoses beginning with the date of first hospital visit for NF1 (from 1987 to 2011) and ending at death, emigration, or cutoff of December 31, 2012, whichever occurred first. The total number of person-years in follow-up was 19,076 (men, 8,931 years; women, 10,145 years). Mean length of follow-up was 13.6 years (median, 13.4 years).

Cancer Outcomes

Follow-up for cancer diagnoses through the population-based, country-wide Finnish Cancer Registry²³ was done automatically using patient personal identity codes as a key. We refer to cancers with ICD-10 codes C47, C48-49, and C70-72—cancers of autonomic nervous system, soft tissue, brain, and CNS—as NF1-specific cancers. Our research protocol also included an exhaustive morphologic subtype analysis using International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3). MPNST was identified with ICD-O-3 morphology codes 9540/3 and 9560/3. Dates and causes of death were obtained from Statistics Finland and from the national Population Register Centre. For cancer deaths, we used the definitions of the Finnish Cancer Registry.²⁴

Statistical Methods

SIRs and standardized mortality ratios (SMRs) were calculated as the ratios of observed cases and expected cases. Expected cases were obtained by multiplying the person-years with the corresponding population rate stratified by age, calendar period, and gender. The 95% CIs were based on the assumption that the number of observed cases followed a Poisson distribution, and the homogeneity of the SIRs between groups was tested by using the standard likelihood ratio test in the Poisson regression model.

The age-specific SIR estimates in [Figure 1](#) were smoothed to reduce random variation and to observe nonlinear behavior with cubic splines.²⁵ The cumulative risk for cancer, that is, the probability of developing cancer by a certain age, was estimated by applying competing-risk methods that allowed delayed entry.²⁶ When estimating the cumulative risk of cancer, we defined death as the competing event that would prevent the patient from being diagnosed with cancer, and we estimated cumulative incidence by using a cause-specific hazard method as described by Putter et al.²⁶

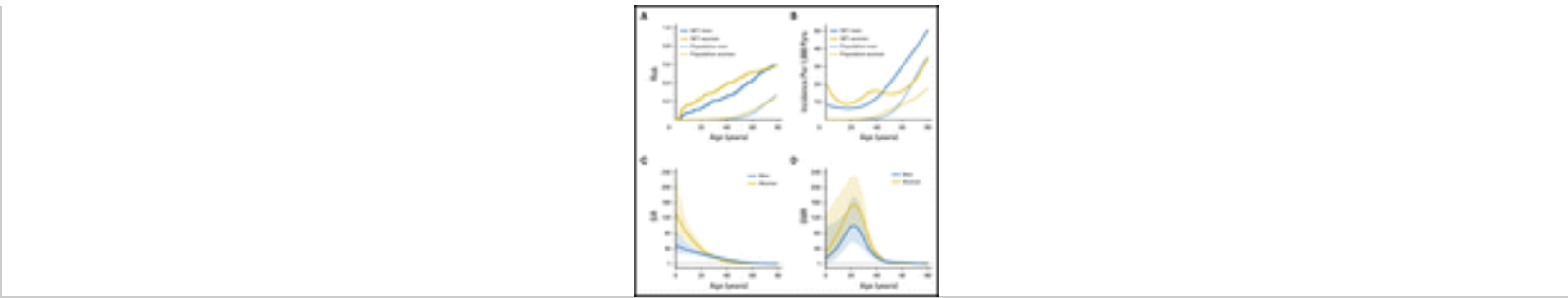


Fig 1. Cancer risk, incidence, and mortality according to age and gender. (A) Cancer risk as a function of age in the neurofibromatosis type 1 (NF1) cohort (solid lines) and general population (dotted lines). The cancer risk of men and women with NF1 is markedly higher than that of the total population. The lifetime risk of cancer in patients with NF1 was estimated to be 59.6%. (B) Cancer incidence per 1,000 person-years (Pyrs) as a function of age in the NF1 cohort and general population. Cancer incidence is higher at all ages in the NF1 cohort compared with the total population. (C) Standardized incidence ratio (SIR) according to age; 95% CIs are shown in shading. SIR of cancer is high at young ages and only trends toward that of the population level at age ≥ 70 years. (D) Standardized mortality ratio (SMR) by age; 95% CIs are shown in shading. SMR was highest at young adulthood from age 15 to 30 years.

Carcinoma-specific survival of patients with NF1 was compared with that of matched controls²⁷ who were patients with cancer from the Finnish Cancer Registry matched by cancer site, gender, diagnosis age (within 6 years or 4 years in the study design from which NF1 cancers were omitted), and diagnosis year (within 10 years or 6 years, respectively). All available controls without NF1 were included (patient characteristics are shown in Appendix [Table A1](#), online only). Controls were weighted such that their distributions of cancer site, gender, age, and time of diagnosis were the same as those for patients with NF1. Cumulative cancer-specific survival proportions with 95% CIs were calculated by using the weighted Kaplan-Meier method. Matched Cox proportional hazards regression model²⁸ was used to test the statistical significance of the differences between groups.

Statistical analyses were conducted with statistical software R version 3.2.2 with popEpi package (version 0.2.1; The R Foundation; <https://www.r-project.org/>).

RESULTS

Cancer Risk in Patients With NF1

Choose 

Cancer risk, incidence, SIR, and SMR as functions of age are shown in [Figure 1](#), and individual patients with cancer at different ages are presented in Appendix [Figure A1](#) (online only). The cumulative risks for cancer in patients with NF1 by the ages of 30 years and 50 years were 25.1% and 38.8%, respectively. The respective percentages in the Finnish population were 0.8% and 3.9% by 30 years and 50 years ([Table 1](#)). In women with NF1, the cumulative risk for cancer by age 50 years was 45.2% and in men was 32.0%. The lifetime risk of cancer in patients with NF1 was estimated to be 59.6%, whereas in the general population it was 30.8% ([Fig 1A](#); [Table 1](#)).

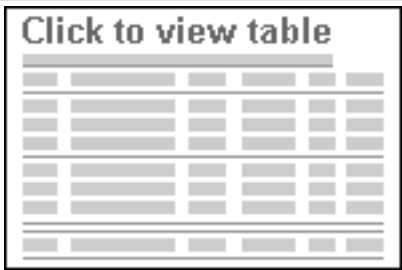


Table 1. Cumulative Risk for Cancer (all sites) and MPNST Among Finnish Patients With NF1 and Cumulative Risk for Cancer in the Finnish Population From 1987 to 2012

General Cancer Incidence in Patients With NF1

An increased incidence of cancer was noted in the NF1 cohort (Fig 1B). A total of 244 cancers was observed, whereas the expected number was 48.5, which resulted in an SIR of 5.03 (95% CI, 4.42 to 5.71; Table 2). Median age at the time of cancer diagnosis was 39 years. SIR was especially high for women in age groups < 30 years (Fig 1C; Table 2). Figure 1C demonstrates high SIR values of cancer in childhood, with a decrease toward that of the general population by age 70 years.

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Table 2. Observed and Expected Numbers of Cancer Cases of All Sites and SIRs With 95% CIs Among Finnish Patients With NF1 During 1987 to 2012

Site-Specific Analysis of Cancers in Patients With NF1

Our data justified three different categories of cancers in patients with NF1. Cancer classes on the basis of SIRs are shown in Appendix [Table A2](#) (online only).

1. MPNSTs and intracranial gliomas, which have high incidence and early onset in patients with NF1. These malignancies are traditionally considered typical for NF1 and are referred to as NF1-specific cancers in the current study. This category includes 63% of all cancers observed in our study.
2. Such malignancies as breast cancer, GIST, and thyroid cancer that display an increased SIR and/or SMR form another category. These are referred to as NF1-related cancers in the current study.
3. Cancers not included in categories 1 or 2 and with an uncertain relationship to NF1 comprise the third category. We did not detect an elevated incidence of these cancers in the NF1 cohort compared with general population.

NF1-specific cancers.

NF1-specific cancers with ICD-10 codes C47, C48-49, and C70-72 were over-represented, especially in young patients. Girls age < 15 years had a markedly higher overall cancer SIR compared with boys ($P = .03$) as shown in [Table 2](#); SIRs for girls and boys were 87.6 and 45.6, respectively. The high SIR for cancer in this youngest age group is largely explained by cancers originating from the CNS. Specifically, of the 47 cancers observed in this age group, 40 originated in the CNS; SIR for CNS cancers in this age group was 186 (95% CI, 134 to 250; $P < .001$).

In the age group composed of patients age 15 to 29 years, the SIRs for all cancers in women and men were 30.8 and 23.0, respectively (Table 2). NF1-specific cancers comprised > 90% of cancers because MPNSTs became more frequent, together with intracranial gliomas, during age 15 to 29 years. However, NF1-specific cancers were not restricted to young age (Appendix Fig A1). SIR for MPNST was 2,056, with 58 observed cases in the entire cohort (Table 3). The cumulative risks for MPNST by age 30 years, age 50 years, and lifetime were estimated to be 8.5%, 12.3%, and 15.8%, respectively (Table 1).

Click to view table

Table 3. Observed and Expected Numbers of Cancer Cases and SIRs With 95% CIs Among Finnish Patients With NF1 from 1987 to 2012, by Cancer Type

Cancer Survival

Cancer survival is shown in [Figure 2](#). The 5-year survival rate of patients with NF1 with cancer of any site was significantly worse ($P = .02$) compared with the survival rate of comparable patients with cancer in the general population ([Fig 2A](#)). In addition, the 5-year survival rate of women with NF1 was significantly worse at 64.3% (95% CI, 55.6% to 74.3%) compared with that of controls at 77.2% (95% CI, 69.8% to 85.5%; $P = .03$). The difference in survival rates between men with NF1 and controls was not significant: 56.2% (95% CI, 46.2% to 68.4%) in the NF1 group versus 57.8% (95% CI, 48.1% to 69.4%) in the control group ($P = .21$; [Fig 2C](#)). When NF1-specific cancers were excluded, survival of patients with cancer with NF1 was decreased compared with controls (54.0% [95% CI, 43.1% to 67.8%] ν 67.5% [95% CI, 57.5% to 79.3%], respectively; $P = .01$; [Fig 2B](#)). Results also suggest that NF1 leads to poorer survival in patients with cancers diagnosed before age 40 years than in controls age < 40 years (62.6% [95% CI, 53.7% to 73.1%] ν 74.4% [95% CI, 66.5% to 83.3%], respectively; $P = .03$; [Fig 2D](#)). When breast cancer survival was analyzed alone, results showed that 5-year survival was poorer in patients with NF1 compared with those without NF1 (67.9% [95% CI, 50.6% to 91.0%] ν 87.8% [95% CI, 75.0% to 100%], respectively; $P = .004$; [Fig 2E](#)).

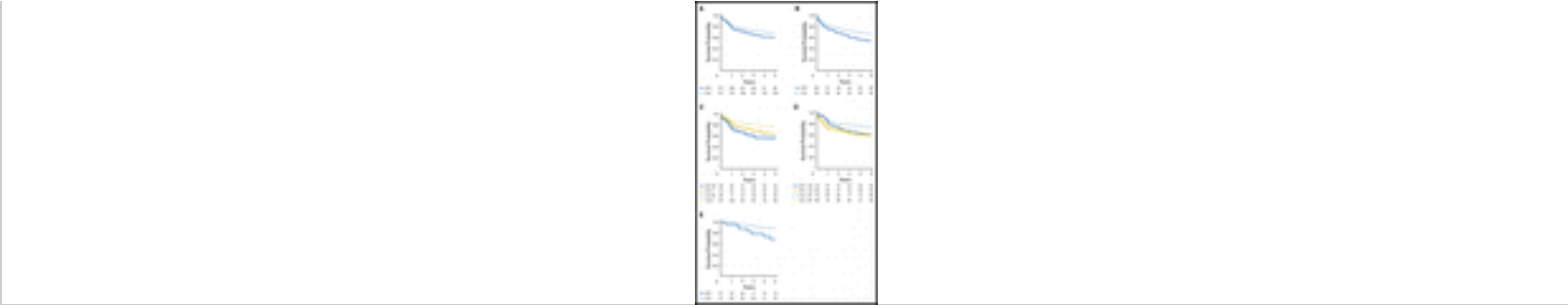


Fig 2.

Cancer survival of patients with neurofibromatosis type 1 (NF1) and matched controls. Numbers of patients at risk and relative numbers of controls (Ctrl) are shown below each graph. (A) The 5-year survival of patients with cancer and NF1 was 60.8% (95% CI, 54.1 to 68.4) versus 68.8% (95% CI, 62.6 to 75.6) in matched controls ($P = .02$). (B) The 5-year survival of patients with cancer and NF1 compared with matched controls was poorer when NF1-specific cancers (International Classification of Diseases, Tenth Revision, codes: C47, C48-49, and C70-72) were excluded (54.0% ν 67.5%, respectively; $P = .01$). (C) For all cancers, the 5-year survival of women (F) with NF1 differed from matched controls (64.3% ν 77.2%, respectively; $P = .03$). The 5-year survival of men (M) with NF1 was 56.2% versus 57.8% in matched controls ($P = .21$). (D) Cancer diagnosis in patients with NF1 age < 40 years led to a poorer survival rate compared with controls age < 40 years (62.6% ν 74.4%, respectively; $P = .03$), although the 1-year survival did not differ from controls. (E) The 5-year survival of patients with NF1 with breast cancer was poorer than that of controls (67.9% ν 87.8%, respectively; $P = .004$).

DISCUSSION

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The higher incidence, increased cumulative cancer risk and mortality, and lower survival in patients with NF1 compared with the general population are clinically important and should determine follow-up practices for patients with NF1. The results are based on virtually complete cancer and death registration systems used in Finland²³ and a population-based NF1 cohort with complete ascertainment.² This cohort realistically represents patients with NF1 in Finland, although persons with mild NF1 or undiagnosed NF1 may not have been included. The cancer risk of the Finnish population is similar to other Western countries and shows no genetic predisposition that could cause bias.²⁹ The results provide a sound overall appreciation of the risk of cancer in patients with NF1. There is a five-fold increase in cancer incidence in the NF1 population, which is the highest cancer incidence yet reported. The estimated cumulative cancer risk in patients with NF1 by age 30 years was as high as 25.1%, and was 38.8% by age 50 years, whereas the respective percentages in the general Finnish population were 0.8% and 3.9%. This emphasizes that the excess cancer risk of NF1 is most pronounced in patients age < 50 years. The estimated lifetime cancer risk in patients with NF1 was 59.6%, which highlights the importance of lifelong follow-up of these patients.

Our results reveal three additional characteristics of cancer manifestation in patients with NF1. First, NF1-specific cancers include malignancies of the CNS and peripheral nervous system. The results from the present study confirm the enormously increased relative risk of MPNSTs and demonstrate that MPNSTs in patients with NF1 are fatal tumors, with an SMR of > 2,000. We observed a total of 58 cases of MPNST and as many as 41 deaths as a result of this condition during follow-up. The lifetime risk of MPNST was estimated to be 15.8%, which is in line with previous studies.^{12,30} NF1-specific malignancies typically manifest early in life and explain the relative excess in cancer incidence and mortality observed in children and young adults. We did not find a sex difference in the incidence or survival of patients with NF1 and MPNST, unlike that reported for another cohort.³¹ Furthermore, a significantly higher SIR of cancer was observed in girls age < 15 years compared with boys, a finding that was explained by brain tumors, mainly intracranial gliomas, in this age group. This is in accordance with a recent study that reported that sex may influence the clinical outcome of optic gliomas.³² Sex difference in the cancer risk of patients with NF1 has previously been reported in some earlier studies,^{31,33,34} but not in others.^{8,17}

Second, the results revealed NF1-related cancers that display an increased SIR and/or SMR. These malignancies include breast cancer, pheochromocytoma, GIST, malignant fibrous histiocytoma, and thyroid cancer. The latter two have not previously been associated with NF1. SIR for breast cancer in women age < 40 years was 11.1. We believe that this is an important finding and should have an effect on clinical follow-up guidelines for young women with NF1.

The third characteristic of cancer in patients with NF1 is poor survival. Specifically, the survival of women with NF1 was significantly worse than that of controls. The poor cancer survival rate observed in the current study explains in part our previous finding that the lifespan of women with NF1 was markedly shortened compared with that of controls.² It should also be noted that even with the exclusion of NF1-specific cancers, the 5-year survival of patients with cancer with NF1 was worse compared with the of matched controls. This suggests that cancers other than those of the nervous system and soft tissue have less favorable outcomes in NF1 compared with the control population, a finding not previously recognized. In part, these findings are explained by poor survival in NF1 breast cancer.

Several cancer types could not be associated with NF1 in this study. In contrast to findings in previous studies,³⁵ we could not detect an increased incidence of juvenile myelomonocytic leukemia. The number of individual cancer cases and/or follow-up time may have been too limited to allow definite conclusions.

The results of the current study provide an estimate of the cancer risks faced by patients with NF1 during their lifetimes. Specifically, pediatric patients with cancer are mainly diagnosed with brain tumors, whereas adolescents and young adults have an increased risk of MPNSTs. However, the increased risk for MPNST is not limited to young age but remains high throughout life. The risk of breast cancer in patients with NF1 becomes important around age 30 years, and other NF1-related cancers mainly occur in patients around age ≥ 40 years. In age groups > 70 years, the overall cancer risk is comparable to that of the general population.

Our results demonstrate that cancer in patients with NF1 manifests in multiple and previously unrecognized ways. The *NF1* gene may have wider effects on carcinogenesis than suggested previously. The high incidence of various types of cancers in patients with NF1 suggests a role of germline *NF1* tumor suppressor gene mutations in the malignant transformation of cells. Thus, the accumulation of mutations that lead to malignancy may occur earlier in patients with NF1 than in control populations, leading to the increased cancer risk of more cancer types than previously have been observed.

We speculate that the poor cancer survival rate in patients with NF1 may be related to cancer developing in the *NF1* gene–deficient microenvironment; this background may be more permissive to cancer growth and invasion. The mutation of the *NF1* gene per se may also alter the malignant cell population, leading to aggressive behavior of the malignancy. We conclude that *NF1* germline and somatic mutations may contribute to human cancer in general, far beyond the NF1 syndrome itself.

[illegible]

All observed cancer cases by age and cancer site (based on International Classification of Diseases Tenth Revision codes) during follow-up 1987-2012. The NF1-specific cancer cases are represented in blue and all other cancer cases in gold. NF1, neurofibromatosis type 1.

Table A1. Distributions of the Observed Cancers From the FCR and NF1 Cohort by Sex, Diagnosis Time Period, and Diagnosis Age Group

Table A2. Observed and Expected Numbers of Cancer Cases, SIRs With 95% CIs, *P* Value, and Site-Specific Probability in Percentage of Cancer Type to Belong to High-, Elevated-, and Low-Risk Categories Among Finnish Patients With NF1 From 1987 to 2012, by Cancer Type

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Manuscript writing: All authors

Final approval of manuscript: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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GLOSSARY TERMS

carcinoma-specific survival:	survival period spanning the time from surgery to death resulting from cancer.
cumulative risk:	a measure of risk of an event (usually disease occurrence) during a specified time period.
malignant peripheral nerve sheath tumor (MPNST):	an aggressive soft tissue cancer that arises in cells surrounding the peripheral nerves.
NF1* (neurofibromatosis type 1):	a dominant hereditary disease caused by germline mutation of the <i>NF1</i> ** gene. Also known as von Recklinghausen's disease.
standardized incidence ratio:	a comparison measure to compare the incidence of a disease in a small population with the incidence in a larger (general) population. The standardized incidence ratio is obtained by dividing the observed number of cases by the expected number of cases. The expected number is the number of cases that would occur in a population with the same age and sex distribution.

