Research article

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Tumors in patients with neurofibromatosis type 1: a single-center retrospective study

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Abstract

Objective. To investigate the risk and pattern of tumors in italian neurofibromatosis type 1 (NF1) patients.

Materials and Methods. A retrospective single institution case review of 711 patients (seen between March 1992 and February 2018) with NF1 was conducted to identify individuals with diagnoses of both NF1 and neoplasm. NF1-associated tumors have been collected and analyzed.

Results. We identified 221 tumors in 191 subjects with a percentage of 26.9%, diagnosed at a median age of 32.5 years (range, 0.6-70.1 years); 111 of these patients were females (58%) and all were followed up for a median of 5.3 years. The cumulative risks for tumor in patients with NF1 by the ages of 30 and 60 years were 10% and 42.5%, respectively. In our patients with tumor, overall survival at 70 years was significantly shorter than in those without it (50% vs 95%, P<0.0001). We found an unequivocally increased incidence for breast cancer in females (33 cases observed).

Conclusions. Tumors that develop in patients with NF1 are heterogeneous, our data are consistent with other reports suggesting an increase in some cancers risk among these individuals, therefore systematic medical follow-up in people with NF1 is important. ***Clin Ter 2022; 173 (2):135-140 doi: 10.7417/CT.2022.2407***

Key words: *neurofibromatosis, cancer, epidemiology, neurofibromin*

Introduction

Neurofibromatosis type 1 (NF1), formerly called von Recklinghausen disease, is a rare genetic disorder with an autosomal dominant transmission and an estimated incidence of 1:2500-3000 live birth. In about 50% of individuals, the disease is caused by a spontaneous mutation. NF1 gene that maps on chromosome 17q11.2, is characterized by a wide mutational spectrum, with more than 3.000 genomic variants reported so far. The NF1 gene is a tumor suppressor that encodes neurofibromin protein, an important negative regulator of the Ras/mitogen-activated protein kinase (MAPK) pathway, that promotes cell proliferation and inhibits cell apoptosis. Its deficit is associated with the development of benign and malignant tumors (1-6).

This syndrome affects multiple organ systems and has a wide range of variable clinical manifestations; there may be ophthalmologic, musculoskeletal, cardiovascular, gastrointestinal, autoimmune, endocrine, central and peripheral nervous system, and learning alterations (7-14). The main characteristic features are: hyperpigmentary abnormalities of the skin (cafe -au-lait macules and inguinal/axillary freckling), iris hamartomas (Lisch nodules), the growth of benign peripheral nerve sheath tumors (neurofibromas) in the skin and skeletal dysplasias (sphenoid wing dysplasia, long-bone dysplasia) (15-17).

Patients with NF1 have an increased susceptibility to develop tumors such as glioma of the optic pathway, glioblastoma, malignant peripheral nerve sheath tumor (MPNST), breast cancer, sarcoma, leukemia, gastrointestinal stromal tumor (GIST), phaeochromocytoma, duodenal carcinoid tumor and melanoma (18-24). Studies that evaluate in detail the real incidence and characteristics of tumors in NF1 are limited. Uusitalo observed 244 cancers in a cohort of 1404 Finnish patients with NF1; the cumulative risk for cancer in subjects by the ages of 30 and 50 years was 25.1% and 38.8%, respectively (25). Another study of 448 patients with NF1 in the United Kingdom showed a 2.7 times higher risk of cancer compared with the general population, with a cumulative risk of 20% by age 50 years (26). In a pediatric Chinese study of 123 NF1 patients, tumors were observed in 12 cases; the cumulative malignancy risk was estimated to be 12% at 20 years and 16% at 30 years (27).

Tumor is an important component of the NF1 phenotype, and one of the few life-threatening complications, therefore a systematic medical follow-up in patients with NF1 is recommended. It is necessary to have comprehensive estimates for the risk of different individual malignant neoplasms to improve the screening for certain tumors and subsequent treatment of malignancy.

In our study we describe the incidence, the relative cancer risk and the spectrum of tumors in NF1 patients.

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Methods and patients

We conducted a retrospective study of all patients with confirmed NF1 seen in our Rare Skin Disease Center, Policlinico Umberto 1, University of Rome "Sapienza" from March 1992 to February 2018. Diagnosis of NF1 was made according to criteria from the NIH Consensus Conference which require the presence of at least two of the following criteria: 1) six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in post-pubertal individuals; 2) axillary or inguinal freckling; 3) two or more neurofibromas of any type or one plexiform neurofibroma; 4) two or more Lisch nodules; 5) optic pathway glioma; 6) bone dysplasia; or 7) a first-degree relative with NF1 (28). Patients underwent regular follow-up in our department with periodical clinical examinations and instrumental assessment according to the guidelines (29).

In this study, all malignant neoplasms and brain tumors (high- and low-grade) were included as "malignancies". Data and clinical characteristics of patients (as gender, age, the date of first admission for NF1, the date of death or of the last visit, time of diagnosis and distribution of cancer site, development of multiple primary tumors and survival period after diagnosis of malignant tumors) were entered into an Excel (Microsoft, Redmond, WA) spreadsheet and analyzed.

The cumulative frequency of malignancy in NF1 patients at different time points and their overall survival were estimated by the Kaplan-Meier method (30). The overall survival of NF1 patients with and without malignancy was compared by the log rank test. A two-tailed P value of <0.05 was considered statistically significant. Statistical analysis was performed through MedCalc, Version 12.1.4.0 (31).

Results

A total of 711 individuals with NF1 were included in the study cohort (311 males and 400 females, with a median age of 37 years, range, 0.9-82 years); patients had participated in our NF1 surveillance program for a median duration of 4.63 years (range, 0.2-24.6 years). During the follow-up period, two hundred and twenty-one tumors were observed in 191 persons (80 in males and 111 in females) with a percentage of 26.9%. Median age of the patients at the time of cancer diagnosis was 32.5 years (range 0.6-70.1 years). There was no significant difference in the proportions developing malignancy in males and females, ($P = 0.60$). Multiple malignancies were reported in 23 patients (3.2%), in detail: 1 patient developed four tumor forms (astrocytoma, atypical fibroxantoma, MPNST and rhabdomyosarcoma), 4 patients developed three several neoplasms and another 18 people had two types of tumors.

The most commonly observed cancers were brain tumors (85 cases), soft tissue tumors (33 cases) and breast cancers (33 cases) (Tab. 1). MPNSTs were more frequent, together with intracranial gliomas and astrocytoma, between 15 and 30 years old. Other cancer types that showed an increased incidence were GISTs and pheochromocytomas. The cumulative malignancy risk in life in the group of NF1 patients was estimated to be 10% at 30 years and more than 40% at 60 years of age, respectively (Fig. 1). Twenty-seven individuals died during the follow-up for oncological causes out of a total of 35 deaths observed; MPNST was the main form of cancer responsible for death, (10/27). There is a statistically significant difference in life expectancy between NF-1 patients with and without cancer as shown in the figure below, $P < 0.0001$ (Fig. 2).

In detail, at age 70, cancer patients had a survival rate of just over 50% against over 95% of non-cancer NF-1 subjects.

Discussion

NF1 is considered as a tumor predisposition syndrome. NF1 patients are, indeed, at an increased risk of development both benign and malignant tumors which constitute an important cause of their morbidity and mortality (32-35). With the exception of subjects with low-grade gliomas, the clinical course of patients with cancer is generally more unfavorable. The incidence of malignancies among individuals with NF1 is higher than in the general population, but the excess risk has not been precisely estimated. In epidemiological studies in Sweden and Denmark, the risk of malignancy in NF1 has been estimated to be about 4 times that of the general population (36,37); the frequency of malignancy in NF1 in the UK has been reported at 7% by the age of 20 and at 20% by the age of 50, while there is a five-fold increase in cancer incidence in the NF1 finnish population (25,26).

Our results are in agreement with those published in the literature. In particular, we observed a cumulative risk of developing neoplasm of 10% at 30 years and over 40% at 60 years in the subjects analyzed.

The spectrum of NF1 related tumors shows selective patterns. Uusitalo reveals three different categories of cancers in patients with NF1: a) malignancies of the central and peripheral nervous system (NF1-specific cancers), which have high incidence and early onset in patients with NF1, b) breast cancer, pheochromocytoma and GIST, that display an increased standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs), c) neoplasms with an uncertain relationship to NFI, without an elevated incidence in the NF1 cohort compared with the general population (25). Although the types of tumors observed in our patient cohort were heterogeneous, they were similar to the spectrum of tumors reported in many NF1 patients, with brain malignancies and MPNSTs that represented almost half of the neoplasms in our cohort (107/221). These neoplasms are the most common NF1 associated tumor. They have a significantly higher incidence in subjects under 30 years and there is a slight prevalence in women as confirmed by our work (58 vs 49, F/M). In children with NF1, the most common neoplasm is the glioma of the optical pathways that occurs with a frequency of about 15% and the mean age at diagnosis is 6 (4, 38). In our case history we have observed a lower percentage, slightly higher than 8% with 59 cases out of 711 subjects analyzed, in almost all without serious sequelae except for a few patients who had, hydrocephalus, early puberty or a significant loss of vision after surgical or chemotherapy treatments. The risk of symptomatic

Table 1. Tumor observed in 711 patients with NF-1 based on age-group and sex.

Type of Age tumor	0-14	15-30	31-50	51-65	66+	Sex M	F	Total
Glioma of the optic pathway	43	10	6	-	-	27	32	59
Breast cancer	-	-	25	8	-	0	33	33
MPNST	2	13	6	2	2	10	15	25
Astrocytomas	7	12	4	-	-	12	11	23
Phaechromocytoma	2	3	10	2	1	10	8	18
GIST	1	-	8	3	-	4	8	12
Sarcomas	1	1	4	2	-	4	4	8
Thyroid carcinoma	-	1	4	2	-	3	4	7
Urinary organs cancer	-	-	1	4	1	4	2	6
Pancreas-Liver carcinomas	-	2	3	1	-	4	2	6
Gastrointestinal carcinomas	-	1	2	3	-	6	0	6
Lymphoid and Hematopoietic system	2	1	2	-	-	2	3	5
Genital organs cancer	-	-	3	-	1	1	3	4
Melanoma	-	-	-	1	2	3	0	3
Glioblastomas	-	1	2	-	-	3	0	3
Lung	-	-	2	-	-	2	0	2
Larynx	-	-	-	1	-	0	1	1

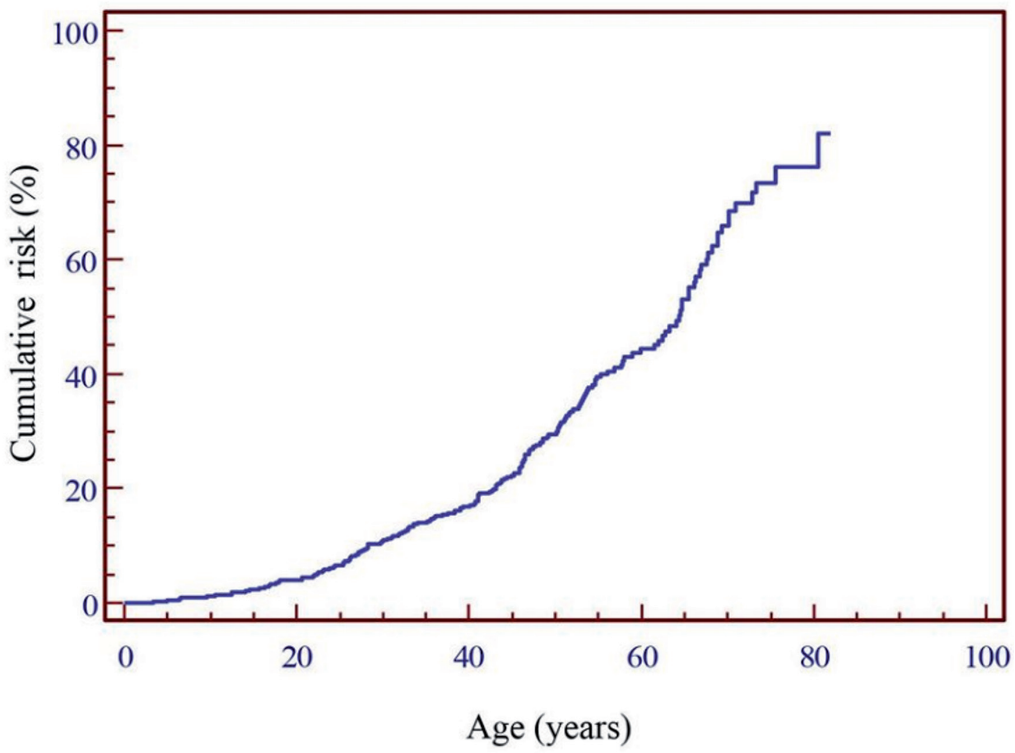

Fig. 1. Cumulative cancer risk in patients with neurofibromatosis type 1 over time.

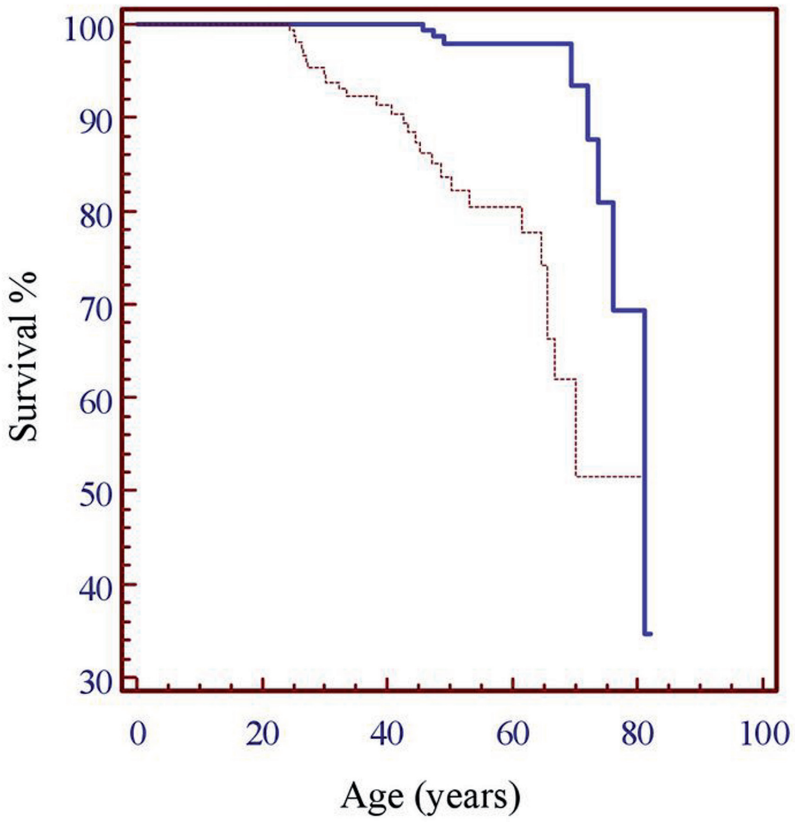

Fig. 2. Overall survival of NF1 patients with (red line) and without malignancy (blue line).

optic glioma is greatest in children under 7 years of age. Elderly patients rarely develop tumors requiring medical intervention. In our patients, 16 cases of optic glioma were observed later when the first brain magnetic resonance imaging (MRI) was performed. Systematic imaging of the optic and cerebral pathways by MRI at the diagnosis of NF1 in young children without symptoms is controversial and should only be requested if an optic glioma is suspected. Gliomas were probably present in our cases many years before our observation.

MPNST is the most frequent malignant tumor associated with NF1 and the risk of developing it during life is 8-13% in NF1 patients. This neoplasm is observed in younger subjects with NF1 compared to the healthy population and it often metastasizes early resulting in a poor prognosis (32). The results of our study confirm a high risk of developing MPNST (25 cases) and an increased probability of death. We have observed that this sarcoma is less likely in pediatric patients, more frequently in adolescents and young adults, but the risk remains high throughout life as shown in Table 1.

Among the NF1-related cancer, such as GIST, pheochromocytoma, breast cancer, soft tissue tumors and thyroid carcinoma, they represented 35% of the malignancies diagnosed in our study (78/221).

Unlike sporadic forms, some types of these cancers have different clinical-pathological characteristics. Most GISTs in NF1 subjects are multiple lesions affecting the small intestine and rarely show mutations in KIT or PDGFRA genes. The risk of developing GIST is 6% in patients with NF-1. These individuals are slightly younger at presentation than the general population (median age 50 years vs 60 years) and about 95% are asymptomatic (40). In our study we observed 12/711 cases (1.7%). Therefore, with a significantly lower incidence than expected, however most cases were diagnosed between age 30 and 50 years in accordance with the literature.

Pheochromocytoma is a rare tumor of the adrenal glands that occurs in 1 to 5.7% of patients with NF1. Its incidence is much higher than the general population (0.002–0.008%). However, it does not show significant differences in the age group of onset which is around the fourth-fifth decade of life as confirmed by our data (18 cases, incidence 2.5%) (41).

Breast cancer has been observed in 33 women. This is an important and alarming element that should have an effect in clinical practice and in the management of the follow-up of these patients. Women with NF-1 have a relative risk comparable to those who have a family history of breast cancer. The same results have been described in the literature with an estimated risk 5 times higher than that of general population, especially in younger women (42-44). Another non-negligible result is the incidence of thyroid cancer, which is not generally associated with this syndrome. We have observed 7 cases and in our opinion this data should suggest greater attention in its research.

Among the malignancy commonly described during NF1, such as myelomonocytic leukemia, we did not observe a higher incidence in our patient cohort. It was, indeed, observed only in 1 subject of age 2 years.

Since the NF1 gene is frequently mutated in sporadic melanoma, it has been supposed that people with NF1 are at higher risk of melanoma (19,33,36). However, we have not found an evidence for an increased risk of melanoma in NF1 people with only three cases, in details a lentigo maligna, a superficial spreading melanoma and an amelanotic nodular melanoma.

Finally, among the very frequent cancers in the general population such as lung cancer, colorectal, prostate cancer, etc, which cannot be classified in the previous groups, we have not observed a higher frequency in NF1 patients than in healthy subjects, confirming the literature data, except for a study conducted in the United Kingdom, which suggested an increased risk of colorectal cancer for individuals under 50 years of age (40). The high incidence of various forms of tumors observed in individuals with NF1 suggests an important role of germline mutations in the NF1 tumor suppressor gene in malignant cell transformation. However, the accumulation of somatic mutations leading to cancer may occur earlier in affected individuals than in the general population.

Overall, the second inactivating mutation of NF1 appears to be a common factor of several tumors in neurofibromatosis, but the complexity of the tumor pathogenesis still needs to be elucidated (46). In addition to the loss of neurofibromin function, further activating aberrations in other important oncogenes involved in other molecular pathways (Ras, MAP kinase, and PI3K-mTOR) may lead to the proliferation of cancer cells. Somatic mutations of the NF1 gene have also been observed in several sporadic tumors. As demonstrated by McPherson et al., the sequencing of the exome of blood cells, of a dermal neurofibroma, of an MPNST and of cells of a breast carcinoma of the same patient with NF1, allowed to identify, in addition to the mutation germline of the NF1 gene, also independent somatic mutations which occurred in the other tumors. This indicated that a second hit of the NF1 gene in different sites, with complete loss of the tumor suppressive function of the neurofibromin, could be an early and decisive event for carcinogenesis but not sufficient and that other different additional mutations are required to induce the development of other tumor forms (47).

Our study shows a statistically significant difference in life expectancy between NF-1 patients with and without cancer, $P < 0.0001$. In detail, at the age of 70, cancer patients had a survival rate of just over 50% against over 95% of non-cancer NF-1 subjects. Current data show the importance of the diagnosis of NF1 and the need to follow up these patients for the early detection of malignancies.

In summary, our results provide an estimate of the risk of developing tumors during life in NF1, as is already evident from the literature. More brain tumors are diagnosed in pediatric patients, while in adolescents and young adults there is a higher risk of MPNST. The risk of a breast cancer in NF1 women becomes important around 30 years, the other types of cancer associated with NF1 are observed around 40 years. In the 70-year-old age group, the general risk of developing cancer is comparable to that of the general population. Some studies reported that females had a higher risk of malignancy than males. We have confirmed this observation, (126 vs 95, F/M) (48).

Multiple primary tumors, synchronous or metachronous, are more common in NF1 patients (about 8%). However, our cohort showed a lower frequency of second primary tumors with 23/711 cases observed (3.2%) (26).

The current work presents some limitations; this is the experience of a single institution, so the data may not be representative of the whole territory. Moreover, compared to national studies reported in other countries, we do not have a registry on malignancies in NF1 patients: this is an important limitation affecting statistical power. Nevertheless, the results found in the current study help to better understand and quantify the relationship between NF1 and malignancies. In fact, to the best our knowledge, this work is the biggest in Italy and one of the largest in the in the world in this field. Further studies are needed to confirm or debated our findings.

Conclusion

The higher incidence of developing tumors, the higher cumulative risk, the higher mortality and the reduced survival of patients with NF1 compared to the general population are clinically important data that should influence the management and follow-up of these subjects. Considering these results, an adequate cancer screening in patients with NF1, in relation to the age of the group, is justified, in order to prevent the onset of an aggressive tumor and improve its life expectancy.

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