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# No significant risk of hematological malignancy in patients with neurofibromatosis type 1: single center study of children and adults

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**Abstract**

Background/Aim: Neurofibromatosis type 1 (NF1) is characterized by the occurrence of multisystem tumors. The objective of this study was to analyze the demographic and oncological profile of 830 NF1-individuals regarding prevalence, type, and spectrum of malignancy. Patients and methods: The medical records of patients diagnosed with NF1 with a median age of 22.1 years (range: 0.8–81.6 years) who were followed up for malignancies from 1999 to 2018 were retrospectively reviewed. Results: The prevalence of malignancy occurring in patients diagnosed with NF1 was 34.8% (289/830). The most common types of neoplasia encompassed tumors strictly associated with NF1, including plexiform neurofibromas (PNF; 200/830; 24.1%) and optic pathway gliomas (91/830; 11%). The prevalence of PNFs-transforming to malignant peripheral nerve sheath tumors (MPNST) was 3.5% (7/200). The prevalence of other tumors was 4.8% (40/830). One patient was diagnosed with acute myeloid leukemia (AML), thus the risk of hematological malignancies among all patients with NF1 was 0.1% (1/830). In the population of patients with malignancies, 43/289 (14.9%) individuals were diagnosed with more than one malignancy. Conclusions: The odds ratio (OR) of malignancy in a studied cohort of patients with NF1 was 23 ($p < 0.001$), while the OR of hematological malignancy was 5.1 ($p = 0.1$) in comparison with the general population.



**Keywords:**
hematological malignancy, neurofibromatosis type 1, phacomatosis, optic pathway glioma, brain tumor, acute myeloid leukemia

## Introduction

Neurofibromatosis type 1 (NF1) is one of the most common genetically determined disease and is characterized by 5–15% higher risk of malignant tumor formation than the general population [1]. The NF1-associated *NF1* gene is the tumor suppressor gene. The mutations occurring in NF1-patients cause the inactivation of the gene, predisposing to certain types of tumors arising from the embryonic neural crest [2, 3]. Therefore, there is an association between NF1 and the following malignancy: gliomas, malignant peripheral nerve sheath tumors (MPNSTs), breast cancers, pheochromocytomas, rhabdomyosarcomas, gastrointestinal stromal tumors (GIST), melanomas and certain hematological malignancies, primarily acute myeloid leukemia (AML), and juvenile myelomonocytic leukemia (JMML) [4, 5].

The Phacomatosis Center in Bydgoszcz provides health care for patients with NF1, both children and adults. The objective of this study was to analyze the demographic and clinical profile of NF1-individuals regarding incidence, type, and spectrum of malignancy.

## Patients and methods

### *Data collection*

The medical records of patients diagnosed with NF1 who were followed up in the Phacomatosis Center in the Department of Pediatric Hematology and Oncology in Bydgoszcz from 1999 to 2018 were analyzed. The diagnosis of NF1 was based on the clinical criteria set by the National Institutes of Health (NIH) in patients with at least two of the seven following features: ≥6 *cafe au lait* macules (>0.5 cm in diameter before puberty and >1.5 cm in diameter after puberty), axillary and/or inguinal freckling, ≥2 Lisch nodules (iris hamartomas), ≥2 discrete neurofibromas or ≥1 plexiform neurofibroma (PNF), an optic pathway glioma (OPG), distinctive bony lesions (i.e., long bone dysplasia), and a first-degree relative with NF1 [6]. Medical records of patients were reviewed for demographic and occurrence of malignancies. Due to the retrospective character of the study, the age of patients was determined at the time of analysis. In many cases, there was no information about the age associated with the time of diagnosis of malignancy; therefore this parameter has not been evaluated.

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### *Statistical analysis*

Baseline parameters were compared between groups using Chi-squared or Fisher's exact tests for prevalences. Odds ratio (OR) and 95% confidence intervals (95% CI) were calculated for the differences in prevalence in comparison with general population. Data on the epidemiology of malignancies in Poland in 2015 were taken as a reference denominator [7]. Data analysis was carried out using SPSS 25 (IBM SPSS Statistics, Version 25.0) and Epi-Info (Version 7.2.1.0). Statistical significance was regarded as $p < 0.05$.

## Results

### *Demographics and oncological profile*

A total number of 830 patients diagnosed for NF1 were referred to the Phacomatosis Center from 1999 to 2018, including 454 females (54.7%) and 376 males (45.3%), with a median age of 22.1 years (range: 0.8–81.6 years). The localized cutaneous neurofibromas were not included in the analysis. The prevalence of malignancy occurring in patients diagnosed for NF1 was 34.8% (289/830). Types of malignancies and characteristics of affected patients are presented in table I. As expected, tumors strictly associated with NF1, such as OPGs and PNFs, were the most common in our study group. The prevalence of other than OPGs, PNFs and MPNSTs malignancies in NF1-individuals was 4.8% (40/830), and the median age of these patients was 28.8 years. The prevalence of malignancies required oncological treatment (excluded low-grade OPGs and non-aggressive PNFs) in analyzed patients was 8.9% (74/830). The distribution of these tumors is shown in figure 1. One patient was diagnosed with AML; thus, the risk of hematological malignancies among all patients with NF1 was 0.1% (1/830). In addition, one patient developed severe aplastic anemia at the age of 17 years. In the population of patients with malignancies, 43/289 (14.9%) individuals were diagnosed for more than one malignancy including two patients with three malignancies (Tab. II). The risk of multiple

***Table I. Characteristics of patients with malignancies***

| Malignancies | | | Number of patients (%) | Age at the time of analysis (years) | Gender |
|---|---|---|---|---|---|
| **SOLID TUMORS** | | | | | |
| PNF (n = 200; 24.1%) | Management | Observation only | 184 (22.2) | 27.8 | M = 91, F = 93 |
| | | Without progression to MPNST, oncological treatment required | 9 (1.1) | 32.5 | M = 2, F = 7 |
| | | With progression to MPNST | 7 (0.8) | 32.4 | M = 2, F = 5 |
| OPG (n = 91; 11%) | Management | Observation only | 73 (8.8) | 18.9 | M = 31, F = 42 |
| | | Oncological treatment required | 18 (2.2) | 14.7 | M = 5, F = 13 |
| Brain tumor, another than OPG | | | 18 (2.2) | 26.4 | M = 8, F = 10 |
| Sarcoma another than MPNST (n = 8; 1%) | Localization | Nasopharynx | 1 (0.1) | 41.0 | M = 0, F = 1 |
| | | Soft tissue of the gluteal region | 1 (0.1) | 27.6 | M = 0, F = 1 |
| | | Abdominal cavity | 1 (0.1) | 57.2 | M = 1, F = 0 |
| | | Testicle | 1 (0.1) | 6.4 | M = 1, F = 0 |
| | | Vagina | 1 (0.1) | 2.6 | M = 0, F = 1 |
| | | Collarbone | 1 (0.1) | 42.3 | M = 1, F = 0 |
| | | Orbital bone | 1 (0.1) | 8.0 | M = 0, F = 1 |
| | | GIST | 1 (0.1) | 56.8 | M = 0; F = 1 |
| Breast cancer | | | 5 (0.6) | 56.8 | M = 0, F = 5 |
| Pheochromocytoma | | | 2 (0.2) | 55.0 | M = 1, F = 1 |
| Adrenal adenocarcinoma | | | 2 (0.2) | 30.4 | M = 1, F = 1 |
| Medullary thyroid cancer | | | 1 (0.1) | 43.9 | M = 0, F = 1 |
| Skin melanoma | | | 1 (0.1) | 28.0 | M = 0. F = 1 |
| Ocular melanoma | | | 1 (0.1) | 43.6 | M = 1, F = 0 |
| Endometrial cancer | | | 1 (0.1) | 54.2 | M = 0, F = 1 |
| Liver cancer | | | 1 (0.1) | 16.5 | M = 1, F = 0 |
| Colorectal cancer | | | 1 (0.1) | 56.7 | M = 1, F = 0 |
| **HEMATOLOGIC MALIGNANCIES** | | | | | |
| AML | | | 1 (0.1) | 7.2 | M = 1, F = 0 |

*PNF – plexiform neurofibroma; MPNST – malignant peripheral nerve sheath tumor; OPG – optic pathway glioma; GIST – gastrointestinal stromal tumor; AML – acute myeloid leukemia; M – male; F – female*

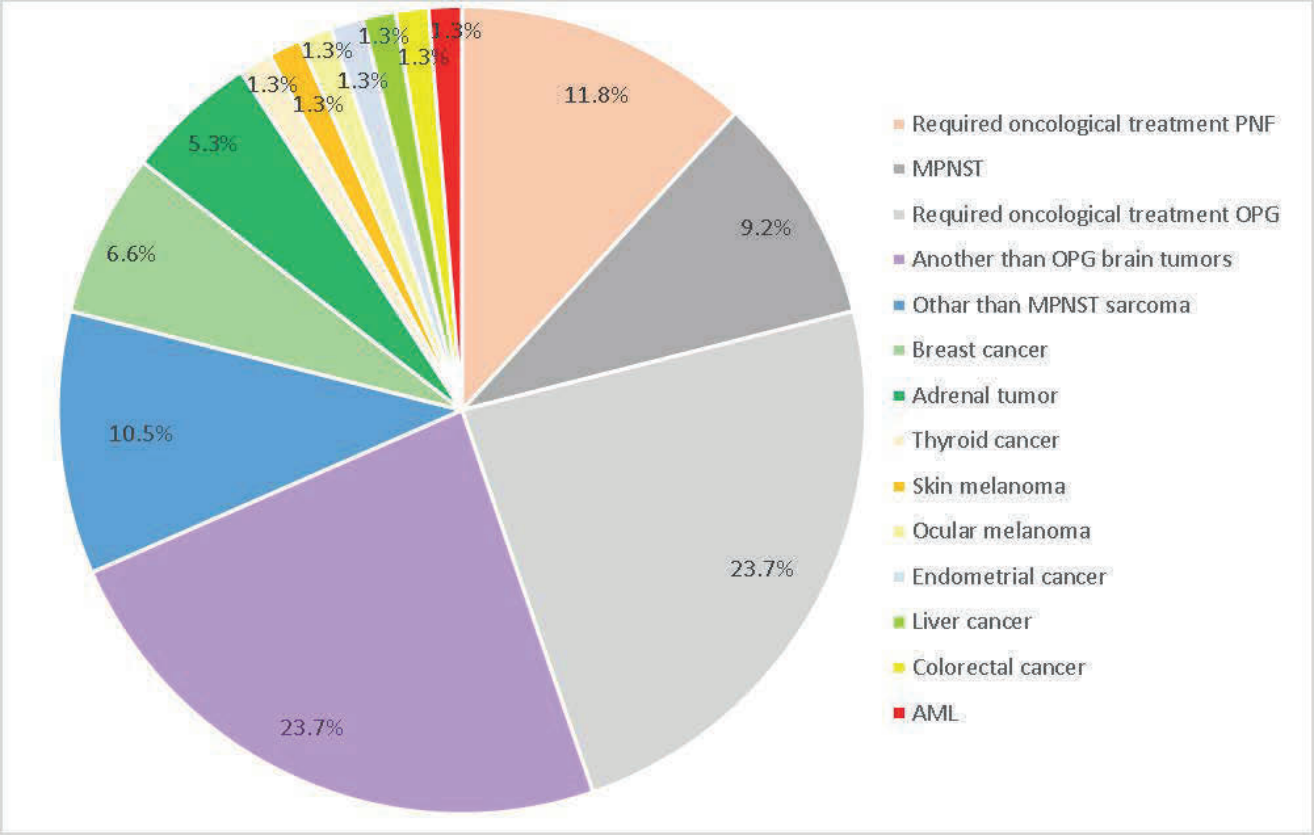


***Fig. 1. The percentage of required oncological treatment different tumor types in NF1-patients***

*PNF – plexiform neurofibroma; MPNST – malignant peripheral nerve sheath tumor; OPG – optic pathway glioma; AML – acute myeloid leukemia*

***Table II. Characteristics of patients with multiple malignancies***

| Malignancies | Number of patients (%) | Age at the time of analysis (years) | Gender |
|---|---|---|---|
| OPG<br>PNF | 27 (3.3) | 26.5 | M = 13, F = 14 |
| PNF<br>Brain cancer (not OPG) | 7 (0.8) | 26.7 | M = 2, F = 5 |
| OPG<br>PNF<br>Ocular melanoma | 1 (0.1) | 43.6 | M = 1, F = 0 |
| Breast cancer<br>Pheochromocytoma<br>GIST | 1 (0.1) | 56.8 | M = 0, F = 1 |
| OPG<br>Testicular sarcoma | 1 (0.1) | 6.4 | M = 1, F = 0 |
| OPG<br>Breast cancer | 1 (0.1) | 45.8 | M = 0, F = 1 |
| PNF<br>Liver cancer | 1 (0.1) | 16.5 | M = 1, F = 0 |
| PNF<br>Nasopharyngeal sarcoma | 1 (0.1) | 41.0 | M = 0, F = 1 |
| PNF<br>Colorectal carcinoma | 1 (0.1) | 56.7 | M = 1, F = 0 |
| PNF<br>Adrenal adenocarcinoma | 1 (0.1) | 33.3 | M = 0, F = 1 |
| Brain tumor (not OPG)<br>Endometrial cancer | 1 (0.1) | 54.2 | M = 0, F = 1 |

*OPG – optic pathway glioma; PNF – plexiform neurofibroma; GIST – gastrointestinal stromal tumor; M – male; F – female*

malignancies in NF1-patients was 5.2% (43/830); however, the risk of multiple malignancies other than OPGs, PNFs, and MPNSTs was 0.2% (2/830).

### *Comparison with the general population*

With the estimated 0.43% (163,281/37.95 million) incidence of malignant diseases in the general Polish population in 2015 and estimated overall number of 1 million patients with malignancies, the OR of malignancy in the studied group of patients with NF1 was 123 (95% CI = 107–142, $p < 0.001$) in comparison with the general population. After exclusion from the analysis of patients with benign malignancies requiring observation with "watch and wait" strategy only (low-grade OPGs and non-aggressive PNFs), the OR of malignancy in NF1-individuals was 23 (95% CI = 18–29; $p < 0.001$) in comparison with the general population. With the estimated number of 9,855 newly diagnosed patients with leukemia or lymphoma in 2015 in Poland, the OR of hematological malignancy in NF1 patients was 5.1 (95% CI = 0.7–36; $p = 0.1$) in comparison with the general population. A comparison of cancer prevalence between patients with NF1 and the general Polish population in particular age groups [7] is presented in figure 2.

## Discussion

It is known that NF1-patients carry a higher risk of developing soft tissue sarcomas, and there is a strong association between NF1 and MPNST [8, 9]. The lifetime risk of MPNST developing in NF1-in-dividuals has been estimated at 8–13%, as compared with 0.001% in the general population [10, 11]. In our cohort, the prevalence of all PNFs was 24.1% (200/830), while the prevalence of PNFs-transforming to MPNST was 3.5% (7/200). The median age of patients with stable PNFs was 27.8 years, so the percentage of patients with malignant transformation can be expected to increase significantly over the next 10–15 years because the median age for NF1-associated MPNST is between 20 and 40 years [12]. In addition to MPNST, we observed other soft tissue sarcoma in patients, mainly rhabdomyosarcoma (RMS). These tumors had various locations, and there were no predispositions for specific age groups. The pathogenesis of RMS in NF1 patients appears even less clear than for MPNST. In the study on a small group of patients, it was observed that RMSs arising in NF1-patients tend to have certain particular characteristics: embryonal histotypes, a pelvic or genitourinary tract locations, and onset in the first decade of life [11]. Other tumors diagnosed in our cohort included bone sarcomas (2/830; 0.2%) and GIST (1/830; 0.1%). The prevalence of all sarcomas was 1.8% (15/830), including non-MPNST sarcoma with a prevalence of 1% (8/830). For comparison, the world incidence rate of sarcomas is 5 per 100,000 individuals in the general population per year [13].

OPGs affect about 15% of patients with NF1 and usually arise during the first decade of life [8, 14]. In our cohort, the prevalence of OPGs was 11%. OPGs were more common among female patients [60% (55/91) vs. 40% (36/91)]. Also more aggressive course of these tumors was observed in females. Oncological treatment due to the progression of OPGs growth was used in 13 female patients and 5 male individuals. The clinical course of NF1-OPGs may be unpredictable, although age and sex of patients have been associated with an increased risk of clinical progression: female patients are more likely to lose vision and require treatment for OPGs than male patients, and girls with optic nerve gliomas are 5–10 times more likely to experience visual decline than boys. In addition, lesions presenting at the age <2 years or after the age of 8–10 years are usually more aggressive than those presenting in children between 2 and 8 years [15].

Young patients with NF1 have up to a 500-fold increased risk of developing myeloid disorders, especially JMML, which is a rare and aggressive form of leukemia, typically diagnosed in early childhood. About 15% of patients with JMML are affected by NF1 [5]. Stiller et

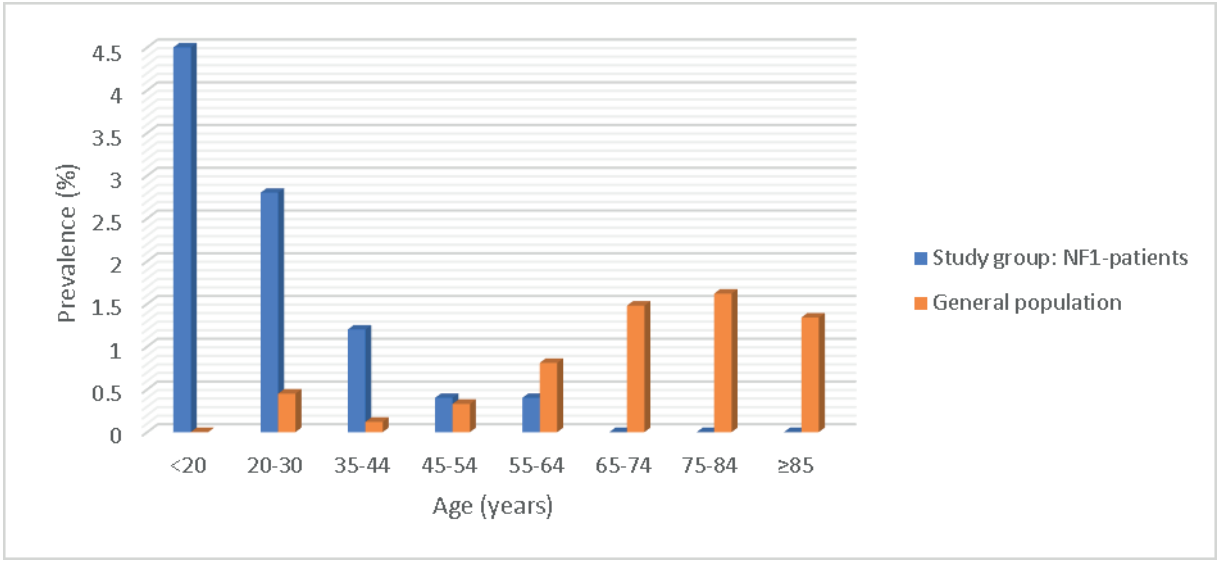


***Fig. 2. Comparison of cancer prevalence between patients with NF1 and the general population in particular age groups***

al. (1994) estimated relative risk to be 224 for the development of myelomonocytic leukemia (MML) in NF1-patients. The relative risks of acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL) were also increased with the values of 5.4 and 10, respectively [16]. Juvenile xanthogranulomas (JXG) were seen with an increased incidence in NF1, and their presence may be associated also with an increased risk of JMML [5]. The existence of lymphoid neoplasms in NF1-patients, particularly diffuse large B-cell lymphoma (DLBCL), has been infrequently reported [5]. In our relatively large cohort, we met only one patient with hematologic malignancy (1/830; 0.1%), and additionally, one child developed aplastic anemia. None of our patients developed JMML.

Somatic mutation of the *NF1* gene was reported in 27.7% of all breast cancers and has been implicated as potential genomic drivers in the development of this carcinoma. Based on a systematic literature review, Suarez-Kelly et al. [17] suggested that female NF1-patients under 50 years have a fivefold increased risk of breast cancer, present with more advanced disease, and may have an increased this cancer-related mortality. In our analysis, the risk of breast cancer in women with NF1 was 4.3-fold higher than in the general Polish population (0.6% vs. 0.14%) [18]. Evans et al. [19] determined the risk of contralateral breast cancer and survival in 142 women with NF1 (median age 46.9 years; range 27.0–84.3 years). The cumulative risk for contralateral breast cancer was 26.5% in 20 years. Five and 10-year overall survival was 64.9% and 49.8% respectively in his study.

Life expectancy in people with NF1 is reduced by about 15 years in comparison with the general population, with malignancy being the most common cause of death [5]. Undoubtedly, the data presented in figure 2 confirm this claim. NF1-individuals develop malignancies earlier when compared to the general population. These patients have a high risk of developing various types of cancer, and the course of treatment is difficult due to the numerous diseases associated with NF1. A more aggressive course of oncological disorders or higher drug resistance is frequently observed.

Currently, a coordinated system of care for patients with NF1 is being created in Poland with the main centers in Bydgoszcz, Warsaw and Gdańsk. This will allow patients to get quick access to diagnostics and treatment. This approach in the long-term period should result in improved quality of life and overall survival of patients with NF1. Vigilant medical care for patients is necessary from an early age. It is very important to spread awareness about the diagnosis and course of NF1 among physicians of all specialties, with distinction for primary care physicians.

### *Authors' contributions*

AM – study concepts and design, data acquisition, analysis and interpretation, manuscript preparation. JS – study design, quality control of data, critical revision of manuscript. AJG – provision of clinical data. All authors – final approval of the manuscript.

### *Conflict of interest*

The authors declare no conflict of interest.

### *Financial support*

None.

### *Ethics*

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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