### Title

Melanocytic neoplasms in neurofibromatosis type 1: a systematic review




### Journal

Melanoma Research, 33(6)

### ISSN

0960-8931



### Authors

Meyer, Summer N

Simmons, Elanee

Studer, Amy C

et al.



### Publication Date

2023-12-01

### DOI

10.1097/cmr.0000000000000912

Peer reviewed

HHS Public Access

Author manuscript

*Melanoma Res*. Author manuscript; available in PMC 2024 December 01.

Published in final edited form as:

*Melanoma Res*. 2023 December 01; 33(6): 437–446. doi:10.1097/CMR.0000000000000912.

# Melanocytic neoplasms in neurofibromatosis type 1: a systematic review

**Summer N. Meyer, BS**[1], **Elanee Simmons, BA**[1,2], **Amy C. Studer, RN, MSN, MSLIS, AHIP**[3], **Katherine A. Rauen, MD, PhD**[4], **Maija Kiuru, MD, PhD**[1,5]

[1]Department of Dermatology, University of California, Davis School of Medicine, Sacramento, CA, USA

[2]Case Western Reserve University School of Medicine, Cleveland, OH, USA

[3]Blaisdell Medical Library, University of California, Davis, Sacramento, CA, USA

[4]Department of Pediatrics, University of California, Davis School of Medicine, Sacramento, CA, USA

[5]Department of Pathology and Laboratory Medicine, University of California, Davis School of Medicine, Sacramento, CA, USA

## Abstract

**Background:** *NF1* is commonly mutated in melanoma, yet the risk of melanoma in individuals with neurofibromatosis type 1 (NF1) is incompletely understood.

**Objectives:** We performed a systematic review to investigate the risk and characteristics of melanoma and melanocytic nevi in NF1 individuals.

**Methods:** PubMed was searched for articles describing NF1 individuals with melanoma and/or melanocytic nevi. Those with cutaneous and ocular melanomas were compared to the general population using SEER data.

**Results:** Fifty-three articles describing 188 NF1 patients were included (melanoma n=82, melanocytic nevi n=93, melanocytic nevi and melanoma n=13). Compared to the general population, NF1 patients with cutaneous melanomas had younger melanoma diagnoses (49.1 vs. 58.6 years, $P = .012$), thicker tumors (3.7 vs. 1.2 mm, $P = .006$), and more frequent disease specific deaths (27.3% vs. 8.6%, $P = .005$) with shorter survival (12.9 vs. 34.2 months, $P = .011$). Ocular melanomas made up 15.0% of all melanomas in NF1 patients versus 1.5% in the general population ($P < .001$). In pooling all population-based studies describing melanoma in NF1 populations, NF1 individuals had 2.55 higher odds of having melanoma compared to the general population. A nevus spilus was commonly reported among NF1 individuals with nevi (44.8%, 39/87).

**Corresponding author contact:** Maija Kiuru, MD PhD, mkiuru@ucdavis.edu, 916-734-6373, 3301 C Street, St 1450, Sacramento, CA 95816, **Reprint requests**: Maija Kiuru, MD, Phd, mkiuru@ucdavis.edu.
S.M. and E.S. contributed equally to this work.

**Conflicts of interest:** The authors have no conflicts of interest to disclose.

**Conclusion:** Our findings suggest that NF1 individuals may have a higher risk for developing melanomas and tend to have thicker melanomas and worse survival compared to the general population, highlighting the importance of cutaneous and ophthalmologic surveillance in NF1 patients. Our review also supports the association between NF1 and nevus spilus.

### Keywords

neurofibromatosis type 1; NF1; von Recklinghausen's disease; melanoma; melanocytic nevi

## Introduction

Neurofibromatosis type 1 (NF1) is an inherited tumor syndrome caused by an autosomal dominant germline mutation in the *NF1* gene. It affects approximately 1 in 3000 individuals and is associated with an increased risk for tumors derived from the neural crest including neurofibromas, malignant peripheral nerve sheath tumors, gliomas, schwannomas, pheochromocytomas, and possibly also melanoma among many others [1–5].

The risk of melanocytic neoplasms in NF1, however, is not fully understood. The prevalence of melanoma among NF1 patients has varied significantly among the limited number of retrospective population-based studies (0.1–5.4%) [1,2,5–15], some of which support an increased risk of melanoma in NF1 while others failed to. Despite this, there has been some biological data in favor of this association. *NF1* is the third most common somatically mutated gene in melanoma, with approximately 12–18% of melanomas and 45–93% of desmoplastic melanomas harboring somatic *NF1* mutations [16–21]. Somatic mutations occur sporadically after conception, whereas germline mutations are present in the germline and passed from parent to offspring (i.e., germline NF1 syndrome). Additionally, the skin of NF1 individuals comprises more melanocytes with greater densities of melanin granules compared to controls, suggesting altered melanocyte biology in NF1 [22–24]. Additionally, the association between NF1 and melanocytic nevi, which are risk factors and potential precursors for melanoma, has not been systematically studied in NF1.

Therefore, we performed a systematic review of the literature to clarify the risk, characterize melanoma and melanocytic nevi in individuals with NF1, and compare the melanoma characteristics found in NF1 to general population estimates obtained from the Surveillance, Epidemiology, and End Results (SEER) Program.

## Methods

### Search strategy, quality assessment, and data extraction

A literature search was performed within PubMed on December 21st, 2021, according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search strategy was created by an academic librarian (A.S.) and peer-reviewed by experts from the UC Davis Library Health Sciences Systematic Review Service. This review was registered on PROSPERO (ID: CRD42022295530). Articles were included if they were peer-reviewed, human studies and contained data on melanoma and/or melanocytic nevi in NF1 individuals. Cohort studies, prevalence studies, and case reports/

series were considered eligible for inclusion. Articles were excluded if the full text was not available in English.

Articles were screened for eligibility by two reviewers (E.S. and S.M.) as outlined in the PRISMA diagram (Figure 1). The titles and abstracts were first screened for relevance, and the second round of screening was based on the articles' full text. Articles were ranked for level of evidence according to The Oxford Centre for Evidence-Based Medicine (version 2, updated in 2011) and assessed for quality using the JBI Critical Appraisal tools for use in Systematic Reviews (2017). The minimum quality assessment score required to be considered a "high quality" article, a threshold pre-determined by the authors, varied by study design as the following: 5/8 for case studies, 6/10 for case series and case controls, and 7/11 for cohort studies. Any scores less were considered "low quality" and excluded from the review. Two blinded authors (S.M. and E.S.) individually assessed the quality of articles, and any disputes were re-evaluated until a consensus was reached. The quality assessment and level of evidence for included studies are included in Table 1.

Excel and the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) was used for the data extraction. Variables related to study type, demographics, NF1, melanoma, and nevi were recorded.

### Statistical Analysis

Characteristics of cutaneous and ocular melanomas were compared between the NF1 cohort and general population estimates obtained from the Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review for 2000–2018 (from 18 registries), after obtaining IRB approval from the University of California, Davis. General population estimates from SEER were limited to the first melanoma occurrence for each patient to avoid duplicate entries. Mucosal (n=3) and CNS melanomas (n=3) were excluded from our comparison to the general population due to having small sample sizes. Those diagnosed with metastatic melanoma with undetected primary lesions were grouped with cutaneous melanomas in the NF1 cohort to match the SEER database (Table 2).

RStudio statistical software version 2021.9.1.372 (Integrated Development for R. RStudio, PBC, Boston, M) and Excel was used for the statistical analysis. Hypothesis tests were two-tailed with a significance level of 0.05. Categorical data was compared using the Pearson's Chi-Squared test with Yates' correction or the Fisher-exact test when cell counts were less than five. Continuous variables were compared with the student's t-test.

## Results

The PubMed search resulted in 737 articles (Figure 1), of which 53 studies (38 case reports, 4 case series, 8 cohort studies, 2 prevalence studies, and 1 case control) describing 188 NF1 individuals with melanocytic neoplasms (melanocytic nevi n=93, melanoma n=82, both melanocytic nevi and melanoma n=13) met inclusion criteria.

### Patient characteristics

Overall, 45 of 104 NF1 patients (43.3%) were male and 59 (56.7%) were female. Familial NF1 was reported in 53.5% (23/43) of patients. The average length of follow up was 2.9 years (SD= 2.4). Two patients had mosaic or segmental NF1. Histological findings were reported for 57 (30.3%) patients. Four of 16 patients (25.0%) reported a family history of melanoma. One hundred (93.5%) patients had a clinical diagnosis of NF1, seven (6.5%) had a genetic diagnosis, and the diagnostic workup was not reported in 81 patients.

### Melanoma subtypes

The melanoma subtypes in NF1 patients (n=95) included cutaneous melanoma (melanoma in situ or MIS 6/95, 6.3%; invasive melanoma 72/95, 75.8%, including 5 cases of metastatic melanoma with unknown primary), ocular melanoma (13/95, 13.7%), mucosal melanoma (3/95, 3.2%), and intracranial melanoma (2/95, 2.1%).

Notably, ocular melanomas made up 15.0% of all melanomas in NF1 patients versus 1.5% in the general population by the number of lesions ($P < .001$, Table 2)

### Invasive cutaneous melanomas in NF1

Of the 72 NF1 patients with invasive cutaneous melanomas (including five cases of metastatic melanoma with unknown primary), 18 (54.5%) were female and 15 (45.5%) were male (compared with 44.0% female and 56.0% male in the general population, $P = .222$; Table 2). The average age of first melanoma diagnoses was 49.1 years (SD= 20.5) compared with 58.6 years (SD=16.5) in the general population ($P = .012$). Sixty-four (95.5%) NF1 patients had a single primary melanoma, and three (4.5%) had multiple (3, 7, and 9 primary tumors). Tumors were located on the face and ears (4/41, 9.8%), scalp and neck (2/41, 4.9%), trunk (16/41, 39.0%), upper extremities (6/41, 14.6%), and lower extremities (13/41, 31.7%) (compared to 12.1%, 7.8%, 34.8%, 26.3%, and 19.1% in the general population, respectively; $P = .172$). The average tumor thickness was 3.7 mm (SD= 4.6), compared with 1.2 mm (SD= 1.2) in the general population ($P = .006$). Seventeen of the cutaneous melanomas in the NF1 cohort were associated with a pre-existing lesion including a neurofibroma in 11 and melanocytic nevi in six. The stage of disease at diagnosis was localized in 62.2% (28/45) of patients, regional in 13.3% (6/45), and distant in 24.4% (11/45), compared with 86.7%, 9.1%, and 4.2% in the general population, respectively ($P < .001$). Of the 22 NF1 patients with data available for status at last follow up, 15 (68.2%) were alive, six (27.3%) died due to their disease, and one (4.5%) died for other reasons, compared with 76.7%, 8.6%, and 14.6% in the general population, respectively ($P = .005$). The mean age of disease specific deaths in the NF1 cohort (n=6) was 38.7 years (SD=24.5) (vs. 65.7 years [SD= 14.6] in the general population, $P = .035$) with an average of 12.9 survival months (SD= 13.0) after diagnosis (vs. 34.0 months [SD= 34.2] in the general population; $P = .011$).

The histological subtypes of cutaneous melanomas included nodular (13.4%, 9/67), superficial spreading (11.4%, 8/67), lentigo maligna (1.5%, 1/67), acral lentiginous (1.5%, 1/67), and other rare subtypes (nevoid/desmoplastic, 3.0%, 2/67); subtype was not specified

for 47 (70.1%). The presence of pigmented epithelioid melanocytes was mentioned in the histologic examination for 10 (30.3%) melanomas in NF1 individuals.

### Ocular melanoma in NF1

Of the 13 NF1 patients with ocular melanomas, nine (75.0%) were female and three (25.0%) were male (vs. 47.4% females and 52.6% males in the general population; $P = .080$) (Table 2), with a mean diagnosis age of 52.3 years (SD= 17.5) (vs. 60.6 years [SD= 15.1] in the general population; $P = .129$). The types of ocular melanomas included uveal melanoma in eight patients (66.7%) and conjunctival melanoma in four (33.3%) (vs. 93.8% and 6.2% in the general population, respectively; $P = .005$). Additionally, three of four patients with conjunctival melanoma had multifocal melanomas, all of which had arisen from primary acquired melanosis. Localized, regional, and distant disease was reported in 76.9%, 15.4%, and 7.7% of NF1 patients (vs. 91.0%, 6.1%, and 2.9% of those in the general population; P =.208). Six of eight (75.0%) NF1 patients were alive at last follow up and two (25.0%) died from their disease (vs. 22.2% disease specific deaths in the general population; P = .855). The mean age of disease specific deaths (n=2) in NF1 was 58.6 years (SD= 6.4) (vs. 67.3 years [SD= 13.8] in the general population; $P = .303$) with an average of 7.0 survival months (SD= 8.5) after diagnosis (vs. 49.4 months [SD= 1.9] in the general population; $P = .091$).

### Melanoma genetics in NF1

Loss of heterozygosity for the *NF1* allele was reported in 2/3 melanomas. $BRAF^{V600E}$ immunohistochemistry was performed on four melanomas, all of which were normal.

### Secondary malignancies in NF1

Secondary malignancies were reported in 11 (20.0%) NF1 patients with a melanocytic neoplasm, including basal cell carcinoma (n=3), breast (n=2), squamous cell carcinoma (n=1), ovarian (n=1), lung (n=1), orbital sarcoma (n=1), renal cell carcinoma (n=1), thyroid (n=1), malignant fibrous histiocytoma (n=1), peripheral malignant nerve sheath tumor (n=1), and pheochromocytoma (n=1).

### Melanoma prevalence in NF1

The prevalence of melanoma in NF1 was summed across all cohort studies found in the literature (147/21913, 0.67%) and compared to the general population prevalence estimates (0.26%) obtained from SEER (Table 3), resulting in a 2.55-fold higher odds (95% CI, 2.17–3.01) of having melanoma for those with NF1 compared to the general population.

### Melanocytic nevi in NF1

Melanocytic nevi were reported in 106 NF1 patients with an average age of onset of 2.9 years (SD=8.2, Table 4). Nevus spilus was the most common nevus type (44.8%, 39/87), followed by dermal melanocytosis (32.2%, 28/87; including slate grey nevus/congenital dermal melanocytosis [28.7%, 25/87] and nevus of Ota [3.4%, 3/87]), common (junctional, intradermal, compound; 12.6%, 11/87) and congenital nevi, including giant congenital melanocytic nevi (11.5%, 10/87), blue nevus (2.3%, 2/87), optic disc melanocytoma (1.1%, 1/87), and choroidal nevus (1.1%, 1/87). Of note, four patients had multiple types of nevi.

For the number of nevi, 78.3% of patients had 1 nevus, 13.0% had 2–10 nevi, and 8.7% had 10–30 nevi.

## Discussion

Our results suggest that individuals with NF1 may be at higher risk for developing melanomas and that melanomas in NF1 are associated with poorer long-term outcomes than in the general population, substantiating previous reports. In comparing our NF1 cohort to the general population using the SEER database from 2000–2018, we found that NF1 patients with cutaneous melanomas developed thicker tumors (3.7 vs. 1.2 mm) with younger ages of melanoma diagnoses (49.1 vs. 58.6 years). Additionally, regional and distant melanoma was more common in NF1 patients, and a greater percentage of patients died from their disease with younger ages of death (38.7 vs. 65.7 years) and shorter survival times (12.9 vs. 34.0 months) than the general population, emphasizing how melanomas may be more aggressive in individuals with NF1.

The findings of our study are comparable to a retrospective study by Guillot et al. (2004) which also found young ages at melanoma diagnoses (median: 33 years), thick tumors (median: 3.2 mm), and a female predominance (10 F to 1 M) among 11 NF1 individuals with cutaneous melanoma, all of which were included in our NF1 cohort [9]. Younger ages of cancer diagnoses, increased mortality, and lower survival has also been reported for other cancers in NF1 [1,9,12,13]. Guillot and colleagues suggested that the thicker tumors found in NF1 patients may be due to the difficulty in detecting these neoplasms among the many other pigmented lesions that NF1 patients typically have [9], which is in agreement with some of our findings. In fact, a significant proportion of the cutaneous melanomas from our NF1 cohort developed in association with nevi and neurofibromas. Therefore, NF1 patients should be monitored for any new or changing cutaneous lesions out of concern for increased risk of malignancy. Although the utility and optimal timing of melanoma screening have not been studied in NF1 individuals, we propose annual skin and ocular exams. Additional studies on the efficacy and timing of screening by age are necessary to make more definitive recommendations.

The prevalence of melanoma in NF1 (0.67%), pooled from all population-based studies found in the literature, was significantly higher than the melanoma prevalence in the general population obtained from the SEER database (0.26%), translating to 2.55-fold increased odds of melanoma in NF1 individuals. This is in agreement with more recent large retrospective cohort studies which found the odds of melanoma to be 2.27 (1.75–2.93), and 3.9 (2.4–6.5) times higher in NF1 individuals (Table 3) [1,2]. Similarly, a population-based record-linkage study reported a 3.6 (95% CI, 2.20–5.60) relative risk of melanoma in NF1 patients matched to a national data set of hospital admissions in England [15].

The majority of the population-based studies support the association between NF1 and melanoma (11/14) [1,2,5–9,11,13–15], while only a few have failed to find an increased risk in NF1 [10,12,25]. One of the latter includes a retrospective cohort by Zhang et al. (2019), which found a 0.12% prevalence of melanoma among 875 NF1 patients in the US [10]. However, over 54% of their NF1 cohort were less than 20 years of age while melanoma

typically affects older adults. In another study that compared the cancer incidence rates between NF1 and the general population using a Finnish Cancer Registry over 25 years (1987–2011), the incidence of melanoma was reported to be 1.58 times higher in NF1 (SIR 1.58, 95% CI, 0.32–4.60) but did not reach statistical significance [12]. Taken together, additional prospective studies with sufficient follow up may be necessary to accurately measure the melanoma prevalence in NF1 patients.

The association between ocular melanomas and NF1 has been suggested based on their common neural crest origin, yet remains debatable in the literature [26]. In our study, ocular melanomas made up a greater proportion of melanomas in the NF1 cohort than in the general population (15.0% vs 1.5%, respectively), supporting the association between the two. In comparing the characteristics of ocular melanomas between those with NF1 and the general population, however, we were not able to detect any statistically significant differences, mainly because the NF1 cohort with ocular melanomas was small. Yet, some notable differences we found was that ocular melanomas were more common in females (75.0%) with NF1 despite being more common in males (52%) in the general population overall [12], which may be a reflection of the higher cancer incidence found in NF1 females compared to their male counterparts [12]. Additionally, since most ocular melanomas observed in our NF1 cohort were associated with primary acquired melanosis or preexisting nevi, the threshold to biopsy any new or concerning pigmented conjunctival lesions should be low in NF1 patients.

Uveal melanoma, accounting for the majority of all ocular melanoma cases, has been reported in approximately 3–5% of NF1 patients [27]. Although mutations of *RAS* or *NF1* are rare in uveal melanoma, activation of the downstream MAPK pathway is remarkably common [28]. Additionally, approximately half of uveal melanomas in non-NF1 patients show reduced expression of neurofibromin, suggesting that *NF1* may play a role in the pathogenesis of some uveal melanomas [29].

Conjunctival melanomas are less frequently observed in NF1 patients, and the literature on its relationship to NF1 is also lacking. While the prevalence of conjunctival melanoma in NF1 patients is not known, there is genetic data to suggest that a relationship may exist. Approximately 33% of conjunctival melanomas harbor somatic mutations in *NF1*, while the remaining majority are caused by other RAS/MAPK genes [30]. Taken together, additional studies are required to clarify the risk of ocular melanomas in NF1 populations.

Finally, our results are suggestive of an association between NF1 and nevus spilus, corroborating preceding reports [8,31]. In our study, nevus spilus was the most common nevus type, occurring in 44.8% of NF1 patients with nevi. Similar findings were reported in a retrospective cohort review that identified a nevus spilus in 35 of 1102 (3.2%) NF1 patients [8]. Although the prevalence of nevus spilus in the general population is not well known, it is estimated to be around 0.2–2.3% [32]. Nevus spilus may also have the potential for malignant transformation, and therefore should be monitored in NF1 individuals.

## Limitations:

Our systematic review on melanoma characteristics in NF1 may be limited by potential publication bias, i.e., case reports published in the literature may be more severe or unique compared to what is typically observed. To mitigate this, we utilized a comprehensive search strategy and quality assessment for each article. Additionally, the sample size of those with NF1 and ocular melanomas was small, and common nevi are likely underreported. Lastly, it is possible that those with NF1 were also accounted for in the general population estimates obtained from SEER. However, because of the large sample size, we do not expect this to significantly affect our results.

## Conclusion:

The results of this study found NF1 individuals to be at 2.55-fold higher risk of developing melanoma of all types, and often with earlier ages of diagnoses, more advanced disease, and worse survival outcomes than the general population. Therefore, we suggest annual skin and ophthalmologic exams for NF1 patients. The efficacy and optimal timing of melanoma screening in NF1 patients is not known, and additional studies are needed to make conclusive recommendations. Additionally, our results support the association between NF1 and nevus spilus, which carries a small risk of malignant transformation requiring monitoring.

## Acknowledgements:

We would like to thank the UC Davis Health Clinical and Translational Science Center for their assistance with the statistical analysis.

### Funding/Support:

This study was funded, in part, by the 2023 Medical Student Research Grant from the Melanoma Research Foundation, the National Institute of Arthritis and Musculoskeletal and Skin Diseases of National Institutes of Health through grant number K23AR074530, and by the National Center for Advancing Translational Sciences, National Institutes of Health, through grant number UL1 TR001860.

## References

1. Landry JP, Schertz KL, Chiang YJ, Bhalla AD, Yi M, Keung EZ, et al. Comparison of Cancer Prevalence in Patients With Neurofibromatosis Type 1 at an Academic Cancer Center vs in the General Population From 1985 to 2020. JAMA Netw Open 2021; 4 (3):e210945. [PubMed: 33734413]
2. Trinh P, Li S, Sarin KY. Neurofibromatosis Type 1 and Risk of Skin Cancer. JAMA Dermatol 2022; 158 (10):1214–1216. [PubMed: 36001333]
3. Evans DG, Howard E, Giblin C, Clancy T, Spencer H, Huson SM, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A 2010; 152a (2):327–332. [PubMed: 20082463]
4. DeBella K, Szudek J, Friedman JM. Use of the national institutes of health criteria for diagnosis of neurofibromatosis 1 in children. Pediatrics 2000; 105 (3 Pt 1):608–614. [PubMed: 10699117]
5. Zöller ME, Rembeck B, Odén A, Samuelsson M, Angervall L. Malignant and benign tumors in patients with neurofibromatosis type 1 in a defined Swedish population. Cancer 1997; 79 (11):2125–2131. [PubMed: 9179058]
6. Brasfield RD, Das Gupta TK. Von Recklinghausen's disease: a clinicopathological study. Ann Surg 1972; 175 (1):86–104. [PubMed: 4621893]

7. Knight WA, 3rd, Murphy WK, Gottlieb JA. Neurofibromatosis associated with malignant neurofibromas. Arch Dermatol 1973; 107 (5):747–750. [PubMed: 4633999]
8. Miraglia E, Moliterni E, Iacovino C, Roberti V, Laghi A, Moramarco A, et al. Cutaneous manifestations in neurofibromatosis type 1. Clin Ter 2020; 171 (5):e371–e377. [PubMed: 32901776]
9. Guillot B, Dalac S, Delaunay M, Baccard M, Chevrant-Breton J, Dereure O, et al. Cutaneous malignant melanoma and neurofibromatosis type 1. Melanoma Res 2004; 14 (2):159–163. [PubMed: 15057048]
10. Zhang M, Bhat T, Gutmann DH, Johnson KJ. Melanoma in individuals with neurofibromatosis type 1: a retrospective study. Dermatol Online J 2019; 25 (11).
11. Rubenstein A, Seitz S, Wallace S, Aron A, Lebwohl M. Increased risk of congenital premalignant melanocytic nevi in neurofibromatosis (abst). . Neurology, 1985. p. 194.
12. Uusitalo E, Rantanen M, Kallionpää RA, Pöyhönen M, Leppävirta J, Ylä-Outinen H, et al. Distinctive Cancer Associations in Patients With Neurofibromatosis Type 1. J Clin Oncol 2016; 34 (17):1978–1986. [PubMed: 26926675]
13. Sørensen SA, Mulvihill JJ, Nielsen A. Long-term follow-up of von Recklinghausen neurofibromatosis. Survival and malignant neoplasms. N Engl J Med 1986; 314 (16):1010–1015. [PubMed: 3083258]
14. Rasmussen SA, Yang Q, Friedman JM. Mortality in neurofibromatosis 1: an analysis using U.S. death certificates. Am J Hum Genet 2001; 68 (5):1110–1118. [PubMed: 11283797]
15. Seminog OO, Goldacre MJ. Risk of benign tumours of nervous system, and of malignant neoplasms, in people with neurofibromatosis: population-based record-linkage study. Br J Cancer 2013; 108 (1):193–198. [PubMed: 23257896]
16. Krauthammer M, Kong Y, Ha BH, Evans P, Bacchiocchi A, McCusker JP, et al. Exome sequencing identifies recurrent somatic RAC1 mutations in melanoma. Nat Genet 2012; 44 (9):1006–1014. [PubMed: 22842228]
17. Hodis E, Watson IR, Kryukov GV, Arold ST, Imielinski M, Theurillat JP, et al. A landscape of driver mutations in melanoma. Cell 2012; 150 (2):251–263. [PubMed: 22817889]
18. Berger MF, Hodis E, Heffernan TP, Deribe YL, Lawrence MS, Protopopov A, et al. Melanoma genome sequencing reveals frequent PREX2 mutations. Nature 2012; 485 (7399):502–506. [PubMed: 22622578]
19. Kiuru M, McDermott G, Berger M, Halpern AC, Busam KJ. Desmoplastic melanoma with sarcomatoid dedifferentiation. Am J Surg Pathol 2014; 38 (6):864–870. [PubMed: 24618614]
20. Wiesner T, Kiuru M, Scott SN, Arcila M, Halpern AC, Hollmann T, et al. NF1 Mutations Are Common in Desmoplastic Melanoma. Am J Surg Pathol 2015; 39 (10):1357–1362. [PubMed: 26076063]
21. Shain AH, Garrido M, Botton T, Talevich E, Yeh I, Sanborn JZ, et al. Exome sequencing of desmoplastic melanoma identifies recurrent NFKBIE promoter mutations and diverse activating mutations in the MAPK pathway. Nat Genet 2015; 47 (10):1194–1199. [PubMed: 26343386]
22. Fitzpatrick TB. Melanin synthesis pathways in the pathogenesis of neurofibromatosis. Adv Neurol 1981; 29:209–211. [PubMed: 6798837]
23. Johnson BL, Charneco DR. Café au lait spot in neurofibromatosis and in normal individuals. Arch Dermatol 1970; 102 (4):442–446. [PubMed: 4990489]
24. Benedict PH, Szabó G, Fitzpatrick TB, Sinesi SJ. Melanotic macules in Albright's syndrome and in neurofibromatosis. Jama 1968; 205 (9):618–626. [PubMed: 4969843]
25. Hope DG, Mulvihill JJ. Malignancy in neurofibromatosis. Adv Neurol 1981; 29:33–56. [PubMed: 6798842]
26. Specht CS, Smith TW. Uveal malignant melanoma and von Recklinghausen's neurofibromatosis. Cancer 1988; 62 (4):812–817. [PubMed: 3135111]
27. Honavar SG, Singh AD, Shields CL, Shields JA, Eagle RC Jr. Iris melanoma in a patient with neurofibromatosis. Surv Ophthalmol 2000; 45 (3):231–236. [PubMed: 11094247]
28. Zuidervaart W, van Nieuwpoort F, Stark M, Dijkman R, Packer L, Borgstein AM, et al. Activation of the MAPK pathway is a common event in uveal melanomas although it rarely occurs through mutation of BRAF or RAS. Br J Cancer 2005; 92 (11):2032–2038. [PubMed: 15928660]

29. Foster WJ, Fuller CE, Perry A, Harbour JW. Status of the NF1 tumor suppressor locus in uveal melanoma. Arch Ophthalmol 2003; 121 (9):1311–1315. [PubMed: 12963615]
30. Scholz SL, Cosgarea I, Süßkind D, Murali R, Möller I, Reis H, et al. NF1 mutations in conjunctival melanoma. Br J Cancer 2018; 118 (9):1243–1247. [PubMed: 29559732]
31. Miraglia E, Fino P, Calvieri S, Giustini S. Nevus spilus in neurofibromatosis type 1: a single center experience. G Ital Dermatol Venereol 2020; 155 (5):691–692. [PubMed: 30295445]
32. Manganoni AM, Pavoni L, Farisoglio C, Sereni E, Calzavara-Pinton P. Report of 27 cases of naevus spilus in 2134 patients with melanoma: is naevus spilus a risk marker of cutaneous melanoma? J Eur Acad Dermatol Venereol 2012; 26 (1):129–130. [PubMed: 22168780]
33. Alessio G, Guerriero S, Albano V, Piscitelli D, Falcone V, Lastella P, et al. Neurofibromatosis type 1 and melanoma of the iris arising from a dysplastic nevus: A rare yet casual association? Eur J Ophthalmol 2021; 31 (3):Np45–np49.
34. Antle CM, Damji KF, White VA, Rootman J. Uveal malignant melanoma and optic nerve glioma in von Recklinghausen's neurofibromatosis. Br J Ophthalmol 1990; 74 (8):502–504. [PubMed: 2117971]
35. Ball NJ, Kho GT. Melanocytic nevi are associated with neurofibromas in neurofibromatosis, type I, but not sporadic neurofibromas: a study of 226 cases. J Cutan Pathol 2005; 32 (8):523–532. [PubMed: 16115049]
36. Barringer CB, Gorse SJ, Rigby HS, Reid CD. Multiple malignant melanomas in association with neurofibromatosis type 1. J Plast Reconstr Aesthet Surg 2006; 59 (12):1359–1362. [PubMed: 17113519]
37. Ben-Izhak O, Groisman GM. Anal malignant melanoma and soft-tissue malignant fibrous histiocytoma in neurofibromatosis type 1. Arch Pathol Lab Med 1995; 119 (3):285–288. [PubMed: 7887787]
38. Bin Amer Y, Al-Khenaizan S. Fatal malignant melanoma in a child with neurofibromatosis type 1. Int J Dermatol 2007; 46 (9):967–970. [PubMed: 17822504]
39. Chen W, Fan PC, Happle R. Partial unilateral lentiginosis with ipsilateral Lisch nodules and axillary freckling. Dermatology 2004; 209 (4):321–324. [PubMed: 15539896]
40. Chew PR, Toh VV, Kotwal A. Challenges in staging and surveillance of patients with neurofibromatosis and cutaneous malignant melanoma. JPRAS Open 2019; 21:19–22. [PubMed: 32158881]
41. Cohen PR. Segmental neurofibromatosis and cancer: report of triple malignancy in a woman with mosaic Neurofibromatosis 1 and review of neoplasms in segmental neurofibromatosis. Dermatol Online J 2016; 22 (7).
42. Croxatto JO, Charles DE, Malbran ES. Neurofibromatosis associated with nevus of Ota and choroidal melanoma. Am J Ophthalmol 1981; 92 (4):578–580. [PubMed: 6794373]
43. Duve S, Rakoski J. Cutaneous melanoma in a patient with neurofibromatosis: a case report and review of the literature. Br J Dermatol 1994; 131 (2):290–294. [PubMed: 7917998]
44. Foley RW, Maweni RM, Fabre A, Healy DG. Aggressive behaviour of metastatic melanoma in a patient with neurofibromatosis type 1. Case Rep Surg 2015; 2015:431943. [PubMed: 25893129]
45. Friedman SM, Margo CE. Choroidal melanoma and neurofibromatosis type 1. Arch Ophthalmol 1998; 116 (5):694–695. [PubMed: 9596516]
46. Gallino G, Belli F, Tragni G, Ferro F, Massone PP, Ditto A, et al. Association between cutaneous melanoma and neurofibromatosis type 1: analysis of three clinical cases and review of the literature. Tumori 2000; 86 (1):70–74. [PubMed: 10778770]
47. Giuffrida R, Uranitsch M, Schmid K, Deinlein T, Favero F, Zalaudek I. Hypomelanotic melanoma detected by the "little red riding hood sign" in a patient with neurofibromatosis type 1. Dermatol Pract Concept 2017; 7 (4):71–73. [PubMed: 29214112]
48. Gupta A, Ram J, Jain IS. Nevus of Ota associated with neurofibromatosis. Ann Ophthalmol 1986; 18 (4):154–155. [PubMed: 3109303]
49. Haddad FS, Jamali AF, Rebeiz JJ, Fahl M, Haddad GF. Primary malignant melanoma of the gasserian ganglion associated with neurofibromatosis. Surg Neurol 1991; 35 (4):310–316. [PubMed: 1901179]

50. Hauth L, Montagna M, Cras P. Stroke-like symptoms and leptomeningeal FLAIR hyperintensity in a neurofibromatosis type 1 patient with primary leptomeningeal melanoma. Acta Neurol Belg 2018; 118 (2):335–336. [PubMed: 29687364]
51. Hida T, Idogawa M, Okura M, Sugita S, Sugawara T, Sasaki Y, et al. Genetic analyses of mosaic neurofibromatosis type 1 with giant café-au-lait macule, plexiform neurofibroma and multiple melanocytic nevi. J Dermatol 2020; 47 (6):658–662. [PubMed: 32246533]
52. Ishii S, Han S, Shiiba K, Mizoi T, Okabe M, Horii A, et al. Allelic loss of the NF1 gene in anal malignant melanoma in a patient with neurofibromatosis type 1. Int J Clin Oncol 2001; 6 (4):201–204. [PubMed: 11706558]
53. Kilgore DA, Sanders R, Uwaydat S. Novel and Unusual Retinal Findings in Two Patients with Neurofibromatosis Type 1. Case Rep Ophthalmol 2020; 11 (3):588–594. [PubMed: 33437232]
54. Koga M, Yoshida Y, Imafuku S. Clinical Characteristics of the Halo Phenomenon in Infants with Neurofibromatosis 1: A Case Series. Acta Derm Venereol 2018; 98 (1):153–154. [PubMed: 28902947]
55. Leoni C, Guerriero C, Onesimo R, Coco V, Di Ruscio C, Acampora A, et al. Melanocytic nevi in RASopathies: insights on dermatological diagnostic handles. J Eur Acad Dermatol Venereol 2021; 35 (1):e83–e85. [PubMed: 32679607]
56. Mastrangelo MJ, Goepp CE, Patel YA, Clark WH Jr. Cutaneous melanoma in a patient with neurofibromatosis. Arch Dermatol 1979; 115 (7):864–865. [PubMed: 110269]
57. Medina Mendez CA, Singh AD. Multifocal melanoma of the conjunctiva in an African American patient with neurofibromatosis type 1. Cornea 2014; 33 (7):750–751. [PubMed: 24699564]
58. Miraglia E, Lopez T, Iacovino C, Calvieri S, Giustini S. Melanoma in neurofibromatosis type 1: an Italian single center experience. G Ital Dermatol Venereol. Italy, 2019: pp. 89–91.
59. Neri I, Lambertini M, Tengattini V, Rivalta B, Patrizi A. Halolike Phenomenon Around a Café au Lait Spot Superimposed on a Mongolian Spot. Pediatr Dermatol 2017; 34 (3):e152–e153. [PubMed: 28523880]
60. Ntala C, Biswas A. Spectrum of Melanocytic Proliferation/Differentiation in a Large Series of Cutaneous Neurofibromas: An Under-Recognized Histopathologic Phenomenon and Potential Clue for Neurofibromatosis Type 1. Am J Dermatopathol 2020; 42 (3):165–172. [PubMed: 31503010]
61. Pellegrini AE, Scalamogna PA. Malignant melanoma with osteoid formation. Am J Dermatopathol 1990; 12 (6):607–611. [PubMed: 2125179]
62. Rehany U, Rumelt S. Iridocorneal melanoma associated with type 1 neurofibromatosis: a clinicopathologic study. Ophthalmology 1999; 106 (3):614–618. [PubMed: 10080223]
63. Rübben A, Bausch B, Nikkels A. Somatic deletion of the NF1 gene in a neurofibromatosis type 1-associated malignant melanoma demonstrated by digital PCR. Mol Cancer 2006; 5:36. [PubMed: 16961930]
64. Rubinstein TJ, Plesec TP, Singh AD. Desmoplastic melanoma of the eyelid and conjunctival melanoma in neurofibromatosis type 1: a clinical pathological correlation. Surv Ophthalmol 2015; 60 (1):72–77. [PubMed: 25233828]
65. Rütten A, Goos M. Nevus spilus with malignant melanoma in a patient with neurofibromatosis. Arch Dermatol 1990; 126 (4):539–540.
66. Salvi PF, Lombardi A, Puzzovio A, Stagnitti F, Tisba M, Gaudinieri A, et al. Cutaneous melanoma with neurofibromatosis type 1: rare association? A case report and review of the literature. Ann Ital Chir 2004; 75 (1):91–95. [PubMed: 15283396]
67. Shah PA, Hassan I, Nafee A. Bathing trunk naevus and neurofibromatosis type 1: a unique association of Friedrich's ataxia. J Indian Med Assoc 2004; 102 (6):327–328. [PubMed: 15636042]
68. Silverman JF, Blahove M, Collins JL, Norris HT. Cutaneous malignant melanoma in a black patient with neurofibromatosis (von Recklinghausen's disease). Am J Dermatopathol 1988; 10 (6):536–540. [PubMed: 3146227]
69. Soon C, Humphreys F, Carr RA. Rectal melanoma arising in association with neurofibromatosis type I. Clin Exp Dermatol 2008; 33 (2):207–209. [PubMed: 18076679]

70. Stacy RC, Kenyon KR, Jakobiec FA, Colby KA. Conjunctival melanoma arising from primary acquired melanosis in a patient with neurofibromatosis type I. Cornea 2010; 29 (2):232–234. [PubMed: 20023582]

71. To KW, Rabinowitz SM, Friedman AH, Merker C, Cavanaugh CP. Neurofibromatosis and neural crest neoplasms: primary acquired melanosis and malignant melanoma of the conjunctiva. Surv Ophthalmol 1989; 33 (5):373–379. [PubMed: 2497540]

72. Wiznia RA, Freedman JK, Mancini AD, Shields JA. Malignant melanoma of the choroid in neurofibromatosis. Am J Ophthalmol 1978; 86 (5):684–687. [PubMed: 102202]

73. Wu HE, Li TN, Jin CL, Liu YB. Neurofibromatosis Type 1 with Becker's Nevus and Nevus of Ota. Indian J Dermatol 2020; 65 (1):81–83. [PubMed: 32029954]

74. Yoshida Y, Ehara Y, Yamamoto O. Melanoma in a patient with neurofibromatosis 1: A single institutional study in Japan. J Dermatol 2020; 47 (8):e302–e303. [PubMed: 32483822]

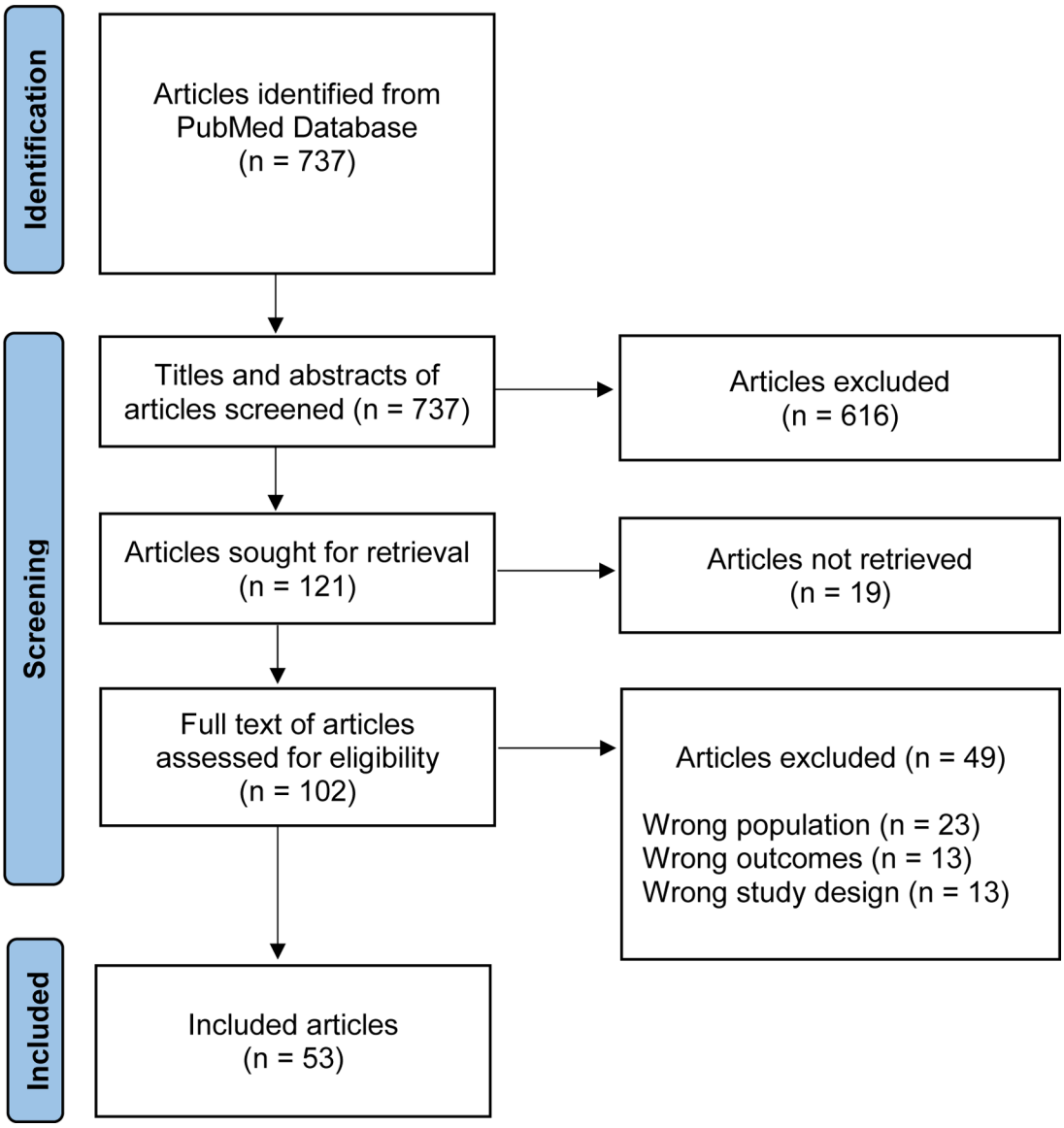


**Figure 1. PRISMA diagram of included studies.**

Our initial literature search within the PubMed database resulted in 737 articles. The titles and abstracts were then screened for eligibility, resulting in 121 articles that were sought for retrieval. Of these, 102 were successfully retrieved and the full texts were screened based on our inclusion criteria. Fifty-three articles describing 188 NF1 patients met our eligibility criteria and were included in our study.

Modified from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

**Table 1.**

Quality assessment and level of evidence of included studies.

| Reference | Study Design | Level of Evidence[a] | Quality consensus score[b] |
|---|---|---|---|
| Alessio et al., 2021[33] | Case report | 5 | 7/8 high quality case report |
| Antle et al., 1990[34] | Case report | 5 | 7/8 high quality case report |
| Ball et al., 2005[35] | Case-control study | 4 | 7/10 high quality case-control study |
| Barringer et al., 2006[36] | Case report | 5 | 7/8 high quality case report |
| Ben-Izhak et al., 1995[37] | Case report | 5 | 7/8 high quality case report |
| Bin Amer et al., 2007[38] | Case report | 5 | 7/8 high quality case report |
| Brasfield et al., 1972[6] | Prevalence study | 3 | 9/9 high quality prevalence study |
| Chen et al., 2004[39] | Case report | 5 | 5/8 high quality case report |
| Chew et al., 2019[40] | Case report | 5 | 7/8 high quality case report |
| Cohen et al., 2016[41] | Case report | 5 | 6/8 high quality case report |
| Croxatto et al., 1981[42] | Case report | 5 | 8/8 high quality case report |
| Duve et al., 1994[43] | Case report | 5 | 6/8 high quality case report |
| Foley et al., 2015[44] | Case report | 5 | 8/8 high quality case report |
| Friedman et al., 1998[45] | Case report | 5 | 6/8 high quality case report |
| Gallino et al., 2000[46] | Case series | 4 | 7/10 high quality case series |
| Giuffrida et al., 2017[47] | Case report | 5 | 6/8 high quality case report |
| Guillot et al., 2004[9] | Case series | 4 | 10/10 high quality case series |
| Gupta et al., 1986[48] | Case report | 5 | 5/8 high quality case report |
| Haddad et al., 1991[49] | Case report | 5 | 8/8 high quality case report |
| Hauth et al., 2018[50] | Case report | 5 | 8/8 high quality case report |
| Hida et al., 2020[51] | Case report | 5 | 6/8 high quality case report |
| Honavar et al., 2000[27] | Case report | 5 | 6/8 high quality case report |
| Ishii et al., 2001[52] | Case report | 5 | 8/8 high quality case report |
| Kilgore et al., 2020[53] | Case report | 5 | 6/8 high quality case report |
| Knight et al., 1973[7] | Cohort study | 3 | 10/11 high quality cohort study |
| Koga et al., 2018[54] | Case series | 4 | 10/10 high quality case series |
| Landry et al., 2021[1] | Cohort study | 3 | 10/11 high quality cohort study |
| Leoni et al., 2021[55] | Prevalence study | 3 | 9/9 for prevalence Studies |
| Mastrangelo et al., 1979[56] | Case report | 5 | 5/8 high quality case report |
| Medina Mendez et al., 2014[57] | Case report | 5 | 7/8 high quality case report |
| Miraglia et al., 2019[58] | Case series | 4 | 10/10 high quality case series |
| Miraglia et al., 2020[8] | Cohort study | 3 | 10/11 high quality cohort study |
| Miraglia et al., 2020[31] | Cohort study | 3 | 9/10 high quality cohort study |
| Neri et al., 2017[59] | Case report | 5 | 5/8 high quality case report |
| Ntala et al., 2020[60] | Cohort study | 3 | 9/11 high quality cohort study |
| Pellegrini et al., 1990[61] | Case report | 5 | 6/8 high quality case report |

| Reference | Study Design | Level of Evidence[a] | Quality consensus score[b] |
|---|---|---|---|
| Rehany et al., 1999[62] | Case report | 5 | 7/8 high quality case report |
| Rübben et al., 2006[63] | Case report | 5 | 5/8 high quality case report |
| Rubinstein et al., 2015[64] | Case report | 5 | 7/8 high quality case report |
| Rütten et al., 1990[65] | Case report | 5 | 5/8 high quality case report |
| Salvi et al., 2004[66] | Case report | 5 | 7/8 high quality case report |
| Seminog et al., 2013[15] | Cohort study | 3 | 9/11 high quality cohort study |
| Shah et al., 2004[67] | Case report | 5 | 5/8 high quality case report |
| Silverman et al., 1988[68] | Case report | 5 | 7/8 high quality case report |
| Soon et al., 2008[69] | Case report | 5 | 7/8 high quality case report |
| Specht et al., 1988[26] | Case report | 5 | 6/8 high quality case report |
| Stacy et al., 2010[70] | Case report | 5 | 7/8 high quality case report |
| To et al., 1989[71] | Case report | 5 | 7/8 high quality case report |
| Wiznia et al., 1978[72] | Case report | 5 | 7/8 high quality case report |
| Wu et al., 2020[73] | Case report | 5 | 5/8 high quality case report |
| Yoshida et al., 2020[74] | Case report | 5 | 5/8 high quality case report |
| Zhang et al., 2019[10] | Cohort study | 3 | 8/11 high quality cohort study |
| Zöller et al., 1997[5] | Cohort study | 3 | 9/11 high quality cohort study |

[a]Articles were ranked for level of evidence according to The Oxford Centre for Evidence-Based Medicine (version 2, updated in 2011) as the following: (1) systematic review of randomized trials or n-of-1 trials; (2) randomized trials or observational study with dramatic effect; (3) non-randomized controlled cohort/follow up study; (4) case-series, case control studies, or historically controlled studies; (5) mechanism-based reasoning.

[b]Quality consensus from two blinded authors that individually assessed the articles using the JBI Critical Appraisal tools for use in Systematic Reviews (2017). The grading criteria and the minimum score required to be considered a “high quality” article, a threshold pre-determined by the authors, varied by study design as the following: 5/8 for case studies, 6/10 for case series and case controls, and 7/11 for cohort studies.

**Table 2.**

Comparison of cutaneous and ocular melanoma characteristics between NF1 and the general population obtained from SEER data.

| **Characteristics, N (%)** | **NF1** | **General population estimates**[a] | **p-value** |
|---|---|---|---|
| **Melanoma subtypes by number of melanomas** [b] | **N= 113** | **N= 676772** | |
| Cutaneous melanoma | | | |
| Invasive melanoma | 78 (69.0) | 383,844 (56.7) | <.001[e] |
| Melanoma in situ | 8 (7.1) | 279,698 (41.3) | |
| Unknown primary with metastatic melanoma[c] | 5 (4.8) | 99 (0.01) | |
| Ocular melanoma | 17 (15.0) | 9947 (1.5) | |
| Mucosal melanoma | 3 (2.7) | 2841 (0.4) | |
| Intracranial melanoma | 2 (1.8) | 69 (0.01) | |
| Other | 0 (0) | 274 (4.0) | |
| **Cutaneous invasive melanoma by patients** [c] | **N= 72** | **N= 272,691** | |
| Male | 15 (45.5) | 152,727 (56.0) | .222[g] |
| Female | 18 (54.5) | 119,964 (44.0) | |
| Unknown sex | 39 | 0 | |
| Age at 1st melanoma dx, mean (SD), y | 49.1 (20.5) | 58.6 (16.5) | .012[f] |
| Tumor thickness, mean (SD), mm | 3.7 (4.6) | 1.2 (2.1) | .006[f] |
| Stage of disease at diagnosis | | | < .001[g] |
| Local | 28 (62.2) | 186,229 (86.7) | |
| Regional | 6 (13.3) | 19,535 (9.1) | |
| Distant | 11 (24.4) | 8924 (4.2) | |
| Unknown | 27 | 58,003 | |
| Follow up, mean (SD), mo | 43.3 (31.4) | 82.5 (63.4) | |
| Status at last follow up | | | .005[e] |
| Alive | 15 (68.2) | 209,274 (76.7) | |
| Melanoma death | 6 (27.3) | 23,554 (8.6) | |
| Non-melanoma death | 1 (4.5) | 39,863 (14.6) | |
| Status not known | 50 | 0 | |
| Disease specific death age, mean (SD), y | 38.7 (24.5) | 65.7 (15.7) | .035[f] |
| Survival months, mean (SD) | 12.9 (13.0) | 34.0 (34.2) | .011[f] |
| Tumor location[d] | | | .172[f] |
| Face/ears | 4 (9.8) | 31,642 (12.1) | |
| Scalp/neck | 2 (4.9) | 20,415 (7.8) | |
| Trunk | 16 (39.0) | 90,955 (34.8) | |
| Upper extremities | 6 (14.6) | 68,683 (26.3) | |
| Lower extremities | 13 (31.7) | 49,930 (19.1) | |

| Characteristics, N (%) | NF1 | General population estimates[a] | p-value |
|---|---|---|---|
| Not specified | 41 lesions | 11,066 | |
| **Ocular melanoma by patients** | **N= 13** | **N= 8,216** | |
| Male | 3 (25.0) | 4323 (52.6) | .080[e] |
| Female | 9 (75.0) | 3893 (47.4) | |
| Unknown sex | 1 | 0 | |
| Stage of disease | | | .208[e] |
| Age of 1st melanoma dx, mean (SD), y | 52.3 (17.5) | 60.6 (15.1) | .129[f] |
| Local | 10 (76.9) | 5446 (91.0) | |
| Regional | 2 (15.4) | 367 (6.1) | |
| Distant | 1 (7.7) | 171 (2.9) | |
| Unknown | 0 | 2232 | |
| Follow up, mean (SD), months | 22.5 (1.6) | 75.7 (59.1) | |
| Status at last follow up | | | .855[e] |
| Alive | 6 (75.0) | 5257 (64.0) | |
| Melanoma death | 2 (25.0) | 1825 (22.2) | |
| Non-melanoma death | 0 (0) | 1099 (13.4) | |
| Death: reason not known | 0 (0) | 35 (0.4) | |
| Status not known | 5 | 0 | |
| Disease specific death age, mean (SD), y | 58.6 (6.4) | 67.3 (13.8) | .303[f] |
| Survival months, mean (SD) | 7.0 (8.5) | 49.4 (1.9) | .091[f] |
| Tumor location | | | .005[e] |
| Uvea | 8 (66.7) | 7289 (93.8) | |
| Conjunctiva | 4 (33.3) | 480 (6.2) | |
| Not specified | 1 | 447 | |

Abbreviation: dx, diagnosis

[a]Data from: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Plus Data, 18 Registries, Nov 2020 Sub (2000–2018) - Linked To County Attributes - Total U.S., 1969–2019 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2021, based on the November 2020 submission. Cutaneous and ocular melanomas from the general population were limited to the first melanoma occurrence to avoid double patient entries.

[b]The proportion of melanoma subtypes was calculated using the total number of primary melanomas per each group.

[c]Unknown primary with metastatic melanoma was grouped with cutaneous invasive melanoma to match the data in the SEER database. There were 5 NF1 patients with unknown primary melanoma with metastatic disease.

[d]Tumor location for those with NF1 was calculated using all melanoma lesions that had data for the tumor location (n=82) among the 72 patients with invasive cutaneous melanomas.

[e]Fisher exact test for count data

[f]Student's t-test for continuous variables

[g]Chi-squared test for count data

**Table 3.**

List of population-based prevalence studies describing melanoma in NF1 populations, with totaled prevalence compared to general population prevalence estimates obtained from SEER.

| Reference | Melanoma prevalence | Estimated risk (95% CI) | Location, study design | Tumor thickness, mm | Age of dx, yr | Metastatic disease (%) | Melanoma types | Limitations |
|---|---|---|---|---|---|---|---|---|
| **Included studies of NF1 populations** | | | | | | | | |
| Brasfield et al. 1972[6] | 6/110 (5.5) | NA | USA, prevalence study | NA | NA | NA | UNS | Cancer centers, small sample size |
| Knight et al. 1973[7] | 1/45 (2.2) | NA | USA, retrospective cohort | NA | 59 M | 1/1 (100) | Cut. | Small sample size, single cancer center |
| Zoller et al. 1997[5] | 1/70 (1.4) | NA | Sweden, cancer registry prospective cohort | NA | 70 M | 0/1 (0) | Cut. | Small sample size |
| Landry et al. 2021[1] | 15/1607 (0.9) | OR 3.9 (2.4–6.5) | USA, retrospective cohort | Mdn: 2.7 (0.9–50.0) | Mdn: 51.8 (34.3–82.5) | 11/15 (73.3) | Cut./ ocular | Single cancer center |
| Miraglia et al. 2020[8] | 7/1102 (0.7) | NA | Italy, retrospective cohort | range: 0–3.5 | NA | NA | Cut. | Single inst. |
| Guillot et al. 2004[9] | 3/671 (0.45) | NA | France, retrospective cohort | Mdn: 3.2 | Mdn: 33 (21–63) | 2/11 (18.2) | Cut. | Cancer centers |
| Seminog et al. 2013[15] | 19/6739 (0.28) | RR 3.6 (2.20–5.60) | UK, population-based record-linkage (cohort) study | NA | NA | NA | Cut. | |
| Zhang et al. 2019[10] | 1/857 (0.12) | NA | USA, retrospective cohort | NA | 47 F | 1/1 (100) | UNS | Large pediatric population, single inst. |
| **Excluded studies of NF1 populations** | | | | | | | | **Reason for exclusion** |
| Trinh et al. 2022[2] | 74/4122 (1.8) | OR 2.27 (1.75–2.93) | US, retrospective cohort | NA | NA | NA | UNS | Published after search date |
| Rubenstein et al. 1985[11] | 4/791 (0.51) | NA | USA, NA | NA | NA | NA | Cut. | Not available in PubMed |
| Uusitalo et al. 2016[12] | 3/1404 (0.21) | NA | Finland, population-based record-linkage study | NA | NA | NA | Cut. | No mention of melanoma in abstract or title |
| Sørensen et al. 1986[13] | 1/212 (0.47) | NA | Denmark, NA | NA | NA | NA | Cut. | No mention of melanoma in the text |
| Rasmussen et al. 2001[14] | 12/3770 (0.32) | PMR 1.2 (1.14–1.28) | USA, based on death records | NA | NA | NA | Cut. | Only included dead participants |
| Hope et al. [25] | 0/395 (0.0) | NA | Sweden, NA | NA | NA | NA | NA | Text not available |
| **Totaled prevalence from all studies compared to the general population (SEER data)** | | | | | | | | |

| Reference | Melanoma prevalence | Estimated risk (95% CI) | Location, study design | Tumor thickness, mm | Age of dx, yr | Metastatic disease (%) | Melanoma types | Limitations |
|---|---|---|---|---|---|---|---|---|
| NF1 | 147/21913 (0.67) | OR 2.55 (2.17–2.99) | NA | NA | NA | NA | NA | NA |
| General population (SEER)[b] | 238178/ 90407820 (0.26) | NA | NA | NA | NA | NA | NA | NA |

Abbreviations: Cut., cutaneous; OR, odds ratio; RR, relative risk; PMR, proportionate mortality ratio; CI, confidence interval; NA, not applicable; UNS, unspecified; inst., institution.

[a] Individual patient data from included studies were only included in our NF1 cohort/data analysis if available.

[b] Data from: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Plus Data, 18 Registries, Nov 2020 Sub (2000–2018) - Linked to County Attributes - Total U.S., 1969–2019 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2021, based on the November 2020 submission.

**Table 4.**

Nevi characteristics in NF1 individuals.

| **Nevi characteristics** | **NF1 (N=106)** |
|---|---|
| **Age of first nevi onset, yrs** [a] | 2.9 (8.2) |
| Not reported | 86 |
| **Nevi type by patient**[b,c] | |
| Nevus spilus | 39 (44.8) |
| Dermal melanocytosis | |
| Congenital dermal melanocytosis | 25 (28.7) |
| Nevus of Ota | 3 (3.4) |
| Common nevi | 11 (12.6) |
| Congenital nevi | 10 (11.5) |
| Blue nevus | 2 (2.3) |
| Optic disc melanocytoma | 1 (1.1) |
| Choroidal nevus | 1 (1.1) |
| Not reported | 19 |
| **Number of nevi** [b] | |
| 1 | 72 (78.3) |
| 2–10 | 12 (13.0) |
| 10–30 | 8 (8.7) |
| Not reported | 14 |
| **Cutaneous nevus location**[b,d] | |
| Face | 5 (6.4) |
| Neck/scalp | 1 (1.3) |
| Trunk | 57 (73.1) |
| Extremities | 19 (24.4) |
| Ocular | 3 (3.8) |
| Not reported | 28 |

[a] Mean (SD)

[b] N (%)

[c] Total does not add up to 100% because four patients had multiple types of nevi.

[d] Total does not add up to 100% because five patients had nevi in multiple different location.