2019

Melanoma in individuals with neurofibromatosis type 1: A retrospective study

May Zhang
Washington University School of Medicine in St. Louis
Trisha Bhat
Washington University School of Medicine in St. Louis
David H. Gutmann
Washington University School of Medicine in St. Louis
Kimberly J. Johnson
Washington University in St. Louis

Melanoma in individuals with neurofibromatosis type 1: a retrospective study

May Zhang[1,2] MD, Trisha Bhat[3] BA, David H Gutmann[4] MD PhD, Kimberly J Johnson[5] MPH PhD

Affiliations: [1]Division of Dermatology, Washington University in St. Louis, St. Louis, Missouri, USA, [2]Department of Dermatology, Hawaii Permanente Medical Group, Wailuku, Hawaii, USA, [3]School of Medicine, Washington University in St. Louis, St. Louis, Missouri, USA, [4]Department of Neurology, Washington University in St. Louis, St. Louis, Missouri, USA, [5]Brown School Master of Public Health Program, Washington University in St. Louis, St. Louis, Missouri, USA

Corresponding Author: Kimberly J. Johnson, MPH, PhD, Brown School Master of Public Health Program, Washington University in St. Louis, 1 Brookings Drive, Campus Box 1196, St. Louis, MO 63130, Email: kijohnson@wustl.edu, Tel: 314-935-9154

Abstract

Background: Neurofibromatosis type 1 (NF1) is a cancer syndrome associated with many different cancer types. There are limited studies examining melanoma risk in this population.

Objective: To identify melanoma cases in NF1 patients and compare melanoma incidence rates relative to a general population sample.

Methods: A retrospective single institution case review of 857 NF1 patients (seen from 7/1997 to 7/2017) was conducted. We calculated age- and calendar period-adjusted standardized incidence ratios (SIRs) for white patients ≥20 years old overall (N=282) and for females (N=156) at their last visit date. We obtained general population melanoma reference rates from the Surveillance, Epidemiology, and End Results (SEER) 9 database.

Results: Among 857 patients, 52.2% were female, 54% were <20 (mean±sd=10.9±4.6) years old, and 46% were ≥20 (40.4±14.9) years old at their last visit date. One white female patient had a malignant melanoma diagnosed at 47 years old. The adjusted SIR was 0.97 (95% CI 0.05-4.78) overall (N=282) and 1.62 (95% CI 0.08-7.98) for females (N=156).

Conclusions: We did not find statistical evidence for an increased melanoma risk in adults with NF1. However, additional large studies are warranted to clarify whether melanoma risk is increased in NF1 patients.

Keywords: malignant melanoma, neurofibromatosis type 1

Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder with a prevalence of approximately 1 in 3,000 [1]. Neurofibromatosis type 1 results from germline mutations in the *NF1* gene encoding the neurofibromin protein. Neurofibromin is a negative regulator of neural crest-derived tissue growth and differentiation. In this regard, *NF1* mutations have been associated with an increased risk of neural crest tumors, including malignant peripheral neural sheath tumors (MPNSTs), peripheral nerve sheath tumors (neurofibromas), and pheochromocytomas. Although melanocytes are also of neural crest origin and the *NF1* gene is a frequently mutated gene in sporadic melanoma [2-3], there is a lack of convincing evidence for an increased risk of malignant melanoma in patients with NF1. Prior case reports have suggested a relationship between melanoma and NF1, but larger population-based studies have not provided clear evidence for an association [4-13]. Given the small number of studies focused on this cancer type in NF1, we sought to evaluate the risk of melanoma in people with NF1.

Methods

A retrospective case review was conducted to identify individuals with NF1 and melanoma following approval by the Washington University Institutional Review Board spanning visits between July 1997 and July 2017. We used a previously compiled neurofibromatosis patient medical record registry [14-15] as the initial patient cohort and added additional patients seen during the expanded study period. We used a REDCap database (https://projectredcap.org/software/) to capture all study data. Patient records, including physician notes (history and physical), patient questionnaires, anesthesia records, outpatient surgery and pre-hospitalization forms, imaging records, administrative notes, and inpatient records, were examined for a documented NF1 diagnosis; patients without a documented NF1 diagnosis were excluded from analysis (N=130). Patient records were also examined for age, sex, race/ethnicity, and reported melanoma or melanoma in situ diagnoses along with the age at diagnosis. For patients with a diagnosis of melanoma, Breslow depth, stage of disease, histological subtype, and clinical course were noted.

To compare risk of melanoma in our NF1 cohort to the general population, age and calendar year standardized incidence ratios (SIRs) were calculated. For this calculation, we only included individuals with a reported race of white and who were ≥20 years old at their last visit (N=282), since melanoma is extremely rare in individuals <20 years of age and in those who are non-white. In addition, we did not observe any melanoma cases in these groups. General population melanoma age-adjusted incidence rates were obtained by sex, age group (20-24, 25-29, 30-34, 35-39, 40-44, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, and ≥80 years), and calendar period (1973-1977, 1978-1982, 1983-1987, 1988-1992, 1993-1997, 1998-2002, 2003-2007, 2008-2012, and 2013-2014) from the Surveillance, Epidemiology, and End Results (SEER) 9 [16] database using SEER*Stat software [17] with selection criteria of white race using the "Race recode (White, Black, Other)" variable and "Melanoma of the Skin" using the "Site recode ICD-O-3/WHO 2008" variable [16].

We calculated age group and calendar period specific person-years at risk for each subject as the person-time contributed to a specific age group calendar period interval starting at age 20 years old using Statistical Analysis Software (Version 9.4, Cary, NC). Person-time was censored in a specific age group calendar period interval if the date of melanoma diagnosis, death, or last follow-up as defined by the visit date of the last record occurred during that interval. The total person-years at risk for each sex in each age group and calendar year interval was multiplied by the corresponding age group and calendar period sex-specific incidence rate from SEER to generate the expected number of cases for that interval. This number was then summed across each age group and calendar year interval to yield the total expected number of melanoma cases in our NF1 cohort for each sex. Finally, the expected

Table 1. *Baseline characteristics of study patients.*

Variable	N (%)
Age category	
< 18 years	432 (50.4)
≥ 18 years	425 (49.6)
Sex	
Male	410 (47.8)
Female	447 (52.2)
Race/Ethnicity	
White	632 (73.8)
Black	184 (21.5)
Hispanic	11 (1.3)
Asian	10 (1.2)
Other/Unknown	20 (2.2)
Melanoma diagnoses	
<18 years	0 (0)
≥18 years	1 (0.1)

number for both sexes summed and for females was divided by the observed number of cases, respectively, to calculate SIRs. Fisher's exact test P values and 95% CIs for the SIRs were calculated using OpenEpi software (http://www.openepi.com/SMR/SMR.htm). A post hoc power calculation was performed in R software version 3.5.0 using the function power.smr.test referenced at https://rdrr.io/github/clayford/bme/man/power.smr.test.html.

Results

A total of 857 patients had a medical record-verified diagnosis of NF1. There were more females than males in the cohort with 447 female (52.2%) and 410 male (47.8%) patients. Four hundred sixty-two (53.9%) patients were <20 years, whereas the remainder were ≥20 years old on the last visit date during the study period. The mean age for those <20 years was 10.9±4.6 years (range 0-19 years) whereas for those ≥20 years was 40.4±14.9 years (range 20-86 years). The distribution of reported race/ethnicity was 73.6% white (N=632), 21.5% black (N=184), 1.3% hispanic (N=11), 1.2% asian (N=10), and 2.3% other or unknown (N=20). A total of 282 patients with NF1 and reported white race who were ≥20 years old (mean±sd=39.4±14.3, range 20-81 years) on their last visit date were included in the SIR calculation. They had a similar sex distribution as the overall group with 156 (55.3%) female and 126 (44.7%) male patients (**Table 1**).

We identified one individual with a malignant melanoma diagnosis in their record among the 857 patients. The patient was a 47-year-old white woman with a history of NF1 diagnosed in childhood, complicated by pheochromocytoma status post right adrenalectomy and a right above the knee amputation due to NF1-associated

Table 2. *Literature review of the association between NF1 and melanoma from studies that calculated prevalence and risk estimates.*

Authors	Publication findings	Prevalence	Risk estimate
Brasfield & Das Gupta [4]	Six melanomas in 110 patients, 3 from giant congenital nevi	5.5%	
Guillot et al. [5]	Eleven patients with melanoma: 3 melanomas in 671 patients at 4 centers with NF1 and melanoma registries and 8 melanomas in an unknown number of patients at an additional 6 centers	0.45%	
Hope et al. [6]	No melanomas identified in 395 patients	0%	
Knight et al. [7]	One melanoma in 45 patients	2.2%	
Rasmussen et al. [8]	Melanoma listed as cause of death in 12 of 3770 NF1 patients compared to cause of death on death certificates in the general population	0.32%	PMR 0.52 (95% CI 0.27-0.90)
Rubenstein et al. [9]	Four melanomas in 791 patients	0.51%	
Seminog et al. [10]	Nineteen melanomas in 6739 NF1 patients compared to rates of melanoma in a linked data set of hospital admissions in England	0.28%	RR 3.60 (95% CI 2.20–5.60)
Sorensen et al. [11]	One melanoma in 212 patients	0.47%	
Uusitalo et al. [12]	Three melanomas in 1404 NF1 patients compared to rates of melanoma in an age, calendar and gender adjusted Finish cohort	0.21%	SIR 1.58 (95% CI 0.32-4.60)
Zoller et al. [13]	One melanoma in 70 patients	1.4%	

PMR = proportional mortality ratio, CI = confidence interval, RR = relative risk, SIR = standardized incidence ratio.

skeletal deformities. She had no history of dysplastic nevi. She initially presented with abdominal pain and vomiting in the emergency room and a CT abdomen and pelvis showed extensive tumors throughout her body including in her lungs, liver, kidneys, and lymph nodes. A biopsy of a right inguinal lymph node was diagnostic for metastatic melanoma with unknown primary, and immunohistochemistry was negative for the $BRAF^{V600}$ mutation. She was started on ipilimumab and got four rounds of therapy before dying from respiratory failure two months after her initial diagnosis.

The age, sex, and calendar year adjusted SIR among the 282 subjects included in the SIR calculation was 0.97 (95% CI 0.05-4.78, P=0.55). For females, the SIR was 1.62 (95% CI 0.08-7.98, P=0.92).

Discussion

The findings described in our study add to previous reports, with no statistically significant evidence for an increased risk of melanoma in the NF1 population. Although there have been many case reports and small case series postulating a link between NF1 and melanoma, larger studies have not consistently revealed statistically significant evidence for an increased melanoma risk in adults with NF1. Seminog et al. [10] found an increased melanoma risk in NF1 patients, with 19 melanoma cases in 6,739 NF1 patients (prevalence 0.28%) and an age, sex, and calendar year adjusted increased relative risk of 3.6 (95% CI 2.2-5.6) versus the general population. However, a large Finnish study by Uusitalo et al. [12] did not find statistical evidence for an increased incidence of melanoma, identifying three patients with melanoma out of 1,404 NF1 patients (prevalence 0.21%), with an age, sex, and calendar-year adjusted SIR of 1.58 (95% CI 0.32-4.60, P=0.67). Other studies noted a prevalence of melanoma in smaller NF1 cohorts ranging from 0-5.5% [4-13].

An increased melanoma risk in NF1 patients is plausible given that *NF1* mutations are found in a subset of sporadic melanomas, especially those associated with chronically sun-damaged skin, older age, desmoplastic type, and higher mutational burden [18-22]. Additionally, *NF1* loss in melanoma has been associated with other mutations in the RAS pathway, including *RAS p21 protein activator 2* (*RASA2*), *PTPN11*, *SOS1*, *RAF1*, and *SPRED1* [17]. This finding suggests that multiple mutations in the RAS pathway may be necessary to progress to malignant melanoma and that the *NF1* mutation alone is not sufficient by itself to cause melanoma.

A possible reason for a lack of strong evidence for an increased melanoma risk in NF1 may reflect decreased sun exposure in this patient population. Although patients with NF1 are not usually counseled to avoid sunlight, they may do so because of physical and mental disabilities as well as social isolation. Johnson et al. [23] found that children with NF1 without orthopedic impairments had decreased participation in a variety of physical and social activities. Feelings of loneliness [24] and social self-consciousness [25] have also been reported in older individuals with NF1. It is possible that the social isolation experienced by many people with NF1 may result in decreased sun exposure, offsetting any increased risk for melanoma that would be expected to occur as a result of a germline *NF1* mutation. Further research is needed to test this hypothesis.

The current study has some limitations. First, there was a large proportion of pediatric patients in the cohort, whereas melanoma predominantly affects older individuals. However, given that increased malignancy risk of NF1 is higher at younger ages,

this study is still relevant in showing no cases of melanoma in a pediatric population. Second, although this is one of the larger studies on this topic, it represents a single institution study that is underpowered. Given our relatively small sample size and confidence intervals for SIRs overall and for females that are compatible with larger risks, we cannot exclude the possibility of an increased risk for melanoma in the NF1 population. A post hoc power calculation indicated 80% power to detect an SIR of 8, which would mark a strongly increased risk of melanoma. Third, owing to the retrospective nature of the study, the dataset may be incomplete if patients were seen outside our institution. However, as a tertiary care center with a large oncology outpatient center, it can be presumed that patients diagnosed with invasive melanoma at outside institutions would be referred back to our institution in some capacity for surgery, oncology, or long-term follow up in a high-risk skin cancer patient.

Conclusion

The findings reported herein contribute to the existing literature on melanoma risk in NF1 patients, which is important when counseling patients with this disorder.

Potential conflicts of interest

The authors declare no conflicts of interests.

References

1. Riccardi VM. Von Recklinghausen neurofibromatosis. *N Engl J Med*. 1981;305:1617–1627. [PMID: 6796886].
2. Gao J, Aksoy BA, Dogrusoz U, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci Signal*. 2013;6(269):pl1. [PMID: 23550210].
3. Cerami E, Gao J, Dogrusoz U, Gross BE, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov*. 2012;2:401-4. [PMID: 22588877].
4. Brasfield RD, Das Gupta TK. Von Recklinghausen's disease: a clinicopathological study. *Ann Surg* 1972;175:86–104. [PMID: 4621893].
5. Guillot B, Dalac S, Delaunay M, et al. French Group of Cutaneous Oncology: Cutaneous malignant melanoma and neurofibromatosis type 1. *Melanoma Res*. 2004;14:159-63. [PMID: 15057048].
6. Hope DG, Mulvihill JJ. Malignancy in neurofibromatosis. *Adv Neurol*. 1981;29:33-56. [PMID: 679884].
7. Knight WA 3rd, Murphy WK, Gottlieb JA. Neurofibromatosis associated with malignant neurofibromas. *Arch Dermatol*. 1973;107:747–50. [PMID: 4633999].
8. Rasmussen SA, Yang Q, Friedman JM. Mortality in neurofibromatosis 1: an analysis using U.S. death certificates. *Am J Hum Genet*. 2001;68:1110-8. [PMID: 11283797].
9. Rubenstein AE, Seitz SC, Wallace S, Aron A M, Lebwohl M. Increased risk of congenital premalignant melanocytic nevi in neurofibromatosis (abst). *Neurology* 1985; 35 (Suppl):194.
10. 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;108:193-8. [PMID: 23257896].
11. Sorensen SA, Mulvihill JJ, Nielsen A. Long term follow-up of von Recklinghausen neurofibromatosis. Survival and malignant neoplasms. *N Engl J Med*. 1986;314:1010–15. [PMID: 3083258].
12. Uusitalo E, Rantanen M, Kallionpää RA, et al. Distinctive Cancer Associations in Patients with Neurofibromatosis Type 1. *J Clin Oncol*. 2016;34:1978-86. [PMID: 26926675].
13. Zoller MET, Rembeck B, Oden A, Samuelsson M, Angervall L. Malignant and benign tumours in patients with neurofibromatosis type 1 in a defined Swedish population. *Cancer*. 1997;79:2125–31. [PMID: 9179058].
14. Ostendorf AP, Gutmann DH, Weisenberg JL. Epilepsy in individuals with neurofibromatosis type 1. *Epilepsia*. 2013;54:1810-4. [PMID: 24032542].
15. Porcelli B, Zoellner NL, Abadin SS, Gutmann DH, Johnson KJ. Associations between allergic conditions and pediatric brain tumors in Neurofibromatosis type 1. *Fam Cancer*. 2016;15:301-8. [PMID: 26666764].
16. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2016 Sub (1973-2014) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2015 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2017, based on the November 2016 submission.
17. Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.3.4.
18. Krauthammer M, Kong Y, Bacchiocchi A, et al. Exome sequencing identifies recurrent mutations in NF1 and RASopathy genes in sun- exposed melanomas. *Nat Genet*. 2015;47:996–1002. [PMID: 26214590].

19. Hodis E, Watson IR, Kryukov GV, et al. A landscape of driver mutations in melanoma. *Cell*. 2012;150:251–63. [PMID: 22817889].
20. Mar VJ, Wong SQ, Li J, et al. BRAF/NRAS wild-type melanomas have a high mutation load correlating with histologic and molecular signatures of UV damage. *Clin Cancer Res*. 2013;19:4589–98. [PMID: 23833303].
21. Nissan MH, Pratilas CA, Jones AM, et al. Loss of NF1 in cutaneous melanoma is associated with RAS activation and MEK dependence. *Cancer Res*. 2014;74:2340–50. [PMID: 24576830].
22. Halaban R, Krauthammer M. RASopathy Gene Mutations in Melanoma. *J Invest Dermatol*. 2016;136:1755–59. [PMID: 27236105].
23. Johnson BA, Sheng X, Perry AS, Stevenson DA. Activity and participation in children with neurofibromatosis type 1. *Res Dev Disabil*. 2014;36C:213-21. [PMID: 25462482].
24. Ejerskov C, Lasgaard M, Østergaard JR. Teenagers and young adults with neurofibromatosis type 1 are more likely to experience loneliness than siblings without the illness. *Acta Paediatr*. 2015;104:604-9. [PMID: 25625197].
25. Smith KB, Wang DL, Plotkin SR, Park ER. Appearance concerns among women with neurofibromatosis: examining sexual/bodily and social self-consciousness. *Psychooncology*. 2013;22:2711-9. [PMID: 23873824].