



# Risk factors for the development of Spitz neoplasms

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## Abstract

**Background/Objectives:** The principal environmental risk factor for conventional nevi and melanomas is ultraviolet exposure. However, little is known about genetic or environmental risk factors for developing Spitz tumors. This study investigates risk factors associated with Spitz neoplasms.

**Methods:** Patients with Spitz tumors seen at Northwestern Memorial Hospital and Lurie Children's Hospital were surveyed with a 16-item questionnaire about environmental and inherited factors. Spitz tumor patients were compared to a pediatric control cohort from a similar clinical setting. This was supplemented with a meta-analysis of genetic and environmental causes of Spitz neoplasms.

**Results:** One hundred and six Spitz and 58 control surveys were obtained and no statistically significant differences in genetic or environmental risk factors were found between Spitz and control groups.

**Conclusion:** Our data and meta-analysis suggest that typical risk factors associated with melanoma are not significantly associated with Spitz tumors. Identification of relevant genetic or environmental risk factors will likely require larger and population-based studies.

## KEYWORDS

melanocytic neoplasms, meta-analysis, risk factors, Spitz, survey

## 1 | INTRODUCTION

It is well recognized that Spitz neoplasms, though featuring histologic similarities to conventional melanoma cytologic atypia, confluent and expansile nesting, pagetoid spread, and mitotic activity, have distinct clinical and genomic characteristics compared to conventional nevi and melanomas, and the vast majority have indolent clinical behavior.<sup>1</sup> While most conventional nevi and melanomas are driven by UV-induced point mutations in genes such as *BRAF* or *NRAS*, many Spitz neoplasms are the result of chromosomal structural rearrangements in genes such as *ALK*, *ROS1*, *NTRK1/3*, *BRAF*,

*RET*, and *MAP3K8* among others, or harbor *HRAS* mutations, and these variants underlie the most recent WHO definition of Spitz neoplasms.<sup>2-4</sup>

Overall, there are few studies investigating epidemiologic risk factors associated with the development of spitzoid neoplasms, hence risk factors for these tumors remain poorly understood, limiting clinical identification of patients more likely to develop spitzoid neoplasms. We constructed a patient survey focused on demographics, environmental exposures, medical history, and family history to investigate risk factors for Spitz neoplasms and performed a meta-analysis of relevant literature.

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## 2 | MATERIALS AND METHODS

Institutional Review Board approval was obtained through Lurie Children's Hospital (2019–2572) and Northwestern University (STU1127). We queried medical records between 01/01/2006 and 03/05/2020 to identify patients with biopsy-proven Spitz tumors, including Spitz nevi (SN), atypical Spitz tumors (AST), and Spitz melanomas (SM). Cases diagnosed as atypical or borderline melanocytic tumors with some spitzoid features were excluded.

We developed a questionnaire to identify environmental and inherited factors potentially related to Spitz neoplasm development (Figure S1), which was completed in clinic via REDCap or paper survey or sent electronically via REDCap. Control surveys ( $n = 58$ ) were obtained from pediatric patients seen in general pediatric dermatology clinic with no history of Spitz neoplasm. All Spitz patients approached were willing to participate in the survey. For controls, patients were screened from general pediatric dermatology clinic to find age-matched controls. Out of 71 control patients approached to complete the survey, 58 (81.7%) agreed and completed the survey.

We completed a literature review of environmental and genetic risk factors related to Spitz neoplasms. We completed a PubMed search using the term "Spitz" along with keywords relating to our survey questions, for example, "race," "ethnicity," and "Fitzpatrick" in addition to "epidemiology," "risk factors," and "review."

Statistical comparisons were performed with RStudio v1.2.5001 (RStudio) and IBM SPSS Statistics Version 27.0 (IBM Corp). Fisher's exact and chi-square tests compared categorical variables. Student's *t*-test was used to compare mean values. Statistical significance was set at  $p < .003$ , adjusted with the Bonferroni correction for 16 hypotheses.

## 3 | RESULTS

We obtained 106 completed Spitz neoplasm patient surveys and 58 completed control patient surveys (Tables 1 and 2), with an average age of 8 years at diagnosis, similar gender distribution, and with >50% of respondents in both groups being Fitzpatrick types I to III. The majority of respondents were Caucasian, with similar proportion of European ethnicity (Tables 1 and 2).

**TABLE 1** Demographic information for survey and control patients

	Control $n = 58$	Spitz $n = 106$
Sex		
Male	33 (56.9%)	50 (47.2%)
Female	25 (43.1%)	56 (52.8%)
Age at diagnosis (years)		
Mean	8.26	8.31
Range	1–18	1–26

Three survey questions addressed UV exposure in subjects. Spitz respondents reported a higher number of sunburns, with more reporting six or more sunburns compared to control patients (13.2% vs. 3.4%,  $p = .095$ ). All participants denied tanning bed use. Patients reported a similar amount of time outside during peak times in the year with most respondents spending less than five hours outdoors daily. There was no difference between groups in response to a variety of other exposures, including smoking exposure, poor air quality, and pesticide use (Table 2).

Medical history was not significantly different in Spitz and control groups; five Spitz patients reported cancer histories (of melanoma, leukemia, osteosarcoma, and neuroblastoma) ( $p = .16$ ). History of immunosuppression including radiation therapy, chemotherapy, stem cell transplant, organ transplant, and history of CT imaging demonstrated no difference between groups.

Sixty-one (57.5%) Spitz respondents and 32 (55.2%) control respondents reported a family history (1st or 2nd degree) of either melanoma, non-melanoma skin cancer, lung, ovarian, breast, pancreatic, or thyroid cancer, including 26.4% of Spitz patients and 32.8% of control patients ( $p = .47$ ) with a family history of melanoma. No association was found with family history of dysplastic nevus syndrome (DNS) ( $p = 1.00$ ).

## 4 | DISCUSSION

Chimeric fusion proteins and truncations have been identified as the primary oncogenic drivers in the majority of Spitz neoplasms; changes such as translocations, inversions, duplications, deletions, and complex rearrangements are distinct from the UV-induced mutations common among conventional melanoma. Likewise, risk factors for developing Spitz neoplasms are expected to be distinct. Our study found no reproducible genetic or environmental risk factors for Spitz neoplasms, which is consistent with the literature.

The predominance of Spitz neoplasms in younger patients is consistent with a mechanism of occurrence distinct from UV mutagenesis, which tends to accumulate with age. The literature suggests that 20% of Spitz neoplasms occur before age 10 and up to 75% occur before age 20.<sup>5–13</sup> Six retrospective reviews report at least 50% of patients as younger than 20 years old.<sup>5,7,8,11,13,14</sup> However, many of these retrospective reviews only report on patients younger than 18-, 20-, or 30-years old. SN do occur in patients of all ages, with some studies documenting their occurrence in skin of older patients.<sup>15</sup>

Patients younger than 10 years old have a higher prevalence of SN, while AST and SM are more commonly found in patients over 10 years old.<sup>16–18</sup> The age difference in SN versus SM was statistically significant in one study.<sup>18</sup> While the driver mutations for most Spitz neoplasms are not UV-related, UV mutagenesis may be involved in the progression of SN to AST and SM. *TERT* promoter mutations, associated with SM, are thought to be UV-induced.<sup>19</sup>

TABLE 2 Demographic, exposure, medical history, and family history survey results of Spitz and control patients

	Control n=58	Spitz n=106	p-value (significance at p<.003)
<b>Demographics</b>			
Race	44 (75.8%)	88 (83.0%)	.113
Caucasian	1 (1.7%)	2 (1.9%)	
Caucasian + Black/African American	0 (0.0%)	6 (5.7%)	
Caucasian + Hispanic/Latin	2 (3.4%)	2 (1.9%)	
Caucasian + Asian	1 (1.7%)	0 (0.0%)	
Caucasian + American Indian	1 (1.7%)	0 (0.0%)	
Black/African American	8 (13.8%)	5 (4.7%)	
Hispanic/Latin	1 (1.7%)	3 (2.8%)	
Asian			
Ethnicity	33 (56.9%)	46 (43.4%)	.87
European	0 (0.0%)	1 (0.9%)	
European + Indian	0 (0.0%)	2 (1.9%)	
European + Middle Eastern	0 (0.0%)	2 (1.9%)	
European + African	0 (0.0%)	7 (6.6%)	
European + North American	0 (0.0%)	1 (0.9%)	
European + N American + S American	0 (0.0%)	1 (0.9%)	
European + N American + C American	1 (1.7%)	0 (0.0%)	
European + South American	0 (0.0%)	2 (1.9%)	
European + Central American	2 (3.4%)	0 (0.0%)	
European + Southeast Asian	1 (1.7%)	3 (2.8%)	
Indian	0 (0.0%)	1 (0.9%)	
Pacific Islands	0 (0.0%)	3 (2.8%)	
Other	0 (0.0%)	2 (1.9%)	
Middle Eastern	1 (1.7%)	0 (0.0%)	
African	15 (25.9%)	34 (32.1%)	
North American	1 (1.7%)	1 (0.9%)	
South American	4 (6.9%)	0 (0.0%)	
Central American			
Fitzpatrick Score	8 (13.8%)	12 (11.3%)	.94
1	20 (34.5%)	35 (33.0%)	
2	14 (24.1%)	32 (30.2%)	
3	11 (19.0%)	19 (17.9%)	
4	5 (8.6%)	7 (6.6%)	
5	0 (0.0%)	1 (0.9%)	
6			
<b>Exposures</b>			
Year Residence Built	12 (20.7%)	29 (27.4%)	.64
>2000	15 (25.9%)	25 (23.6)	
1980-2000	12 (20.7%)	16 (15.1%)	
1960-1979	7 (12.1%)	15 (14.2%)	
1940-1959	5 (8.6%)	3 (2.8%)	
1920-1939	1 (1.7%)	7 (6.6%)	
1900-1919	1 (1.7%)	3 (2.8%)	
<1900	5 (8.6%)	6 (5.7%)	
N/A			
Number of Sunburns	51 (87.9%)	86 (81.1%)	.095
0-3	5 (8.6%)	6 (5.7%)	
3-6	2 (3.4%)	14 (13.2%)	
6-10			
Tanning Bed Use	0 (0.0%)	0 (0.0%)	
Yes	58 (100.0%)	106 (100.0%)	
No			

(Continues)

TABLE 2 (Continued)

	Control n=58	Spitz n=106	p-value (significance at p<.003)
Outdoor Time (hrs/day)	37 (63.8%)	62 (58.5%)	.017
<5	21 (36.2%)	13 (12.3%)	
≥5	0 (0.0%)	31 (29.2%)	
N/A			
Smoking Exposure	51 (87.9%)	90 (84.9%)	.81
No	7 (12.1%)	15 (14.2%)	
Yes	0 (0.0%)	1 (0.9%)	
N/A			
Poor Air Quality	52 (89.7%)	93 (87.7%)	1.00
No	6 (10.3%)	12 (11.3%)	
Yes	0 (0.0%)	1 (0.9%)	
N/A			
Pesticide Exposure (Yes/No)	46 (79.3%)	75 (70.8%)	.44
No	12 (20.7%)	28 (26.4%)	
Yes	0 (0.0%)	3 (2.8%)	
N/A			
Immunosuppression <sup>†</sup>	2 (3.4%)	8 (7.5%)	0.33
Yes	56 (96.6%)	95 (89.6%)	
No	0 (0.0%)	3 (2.8%)	
N/A			
Imaging	50 (86.2%)	94 (88.7%)	.214
None	8 (13.8%)	12 (11.3%)	
CT			
<b>Medical History</b>			
Personal History of Cancer			.16
No	58 (100%)	98 (92.5%)	
Yes	0 (0.0%)	5 (4.7%)	
N/A	0 (0.0%)	3 (2.8%)	
Personal History Cancer Type			.88
None	58 (100%)	98 (92.5%)	
Melanoma	0 (0.0%)	1 (0.9%)	
Leukemia	0 (0.0%)	2 (1.9%)	
Osteosarcoma	0 (0.0%)	1 (0.9%)	
Neuroblastoma	0 (0.0%)	1 (0.9%)	
N/A	0 (0.0%)	3 (2.8%)	
<b>Family History</b>			
Family History of Cancer			.61
No	26 (44.8%)	40 (37.7%)	
Yes	32 (55.2%)	61 (57.5%)	
N/A	0 (0.0%)	5 (4.7%)	
Family History of DNS <sup>‡</sup>			1.00
Yes	3 (5.2%)	2 (1.9%)	
No	55 (94.8%)	47 (44.3%)	
N/A	0 (0.0%)	57 (98.3%)	
Family History of Melanoma			.47
No	39 (67.2%)	77 (72.6%)	
Yes	19 (32.8%)	28 (26.4%)	
N/A	0 (0.0%)	1 (0.9%)	

<sup>†</sup>Radiation therapy, chemotherapy, stem cell transplant, or organ transplant.

<sup>‡</sup>Dysplastic nevus syndrome.

Additionally, since distinction of benign Spitz from melanoma is generally a greater challenge in adults, pathologists may be more likely to use Spitz tumor in adults and SN in children.

The data and literature suggest a slight predominance of spitzoid proliferation in females, with a ratio close to 1.4:1; however, this has been reported as high as 3:1, particularly after age 10–15 years.<sup>6,7,10,12,18,20-24</sup>

Races reported by Spitz patients in the survey included Caucasian, Hispanic/Latin, Asian, Caucasian and Black, Caucasian and Hispanic/Latin, and Caucasian and Asian; and ethnicities included African, Asian, Middle Eastern, North and South American, Australian, and European, with no significant difference compared to the control group. Fitzpatrick score was assessed by predisposition to burn or tan, and 74.5% of Spitz patients surveyed reported Type I-III. Meta-analysis suggests Spitz neoplasms most commonly occur in Caucasians; however, Spitz lesions have traditionally been studied in majority Caucasian cohorts and are thought to be underdiagnosed in Black patients.<sup>5-14,17,18,20-32</sup> Some studies have focused on characterizing Spitz lesions in Hispanic and Black patients.<sup>10,29</sup> Incidence of SN in the predominantly Caucasian countries of the United States, Australia, and the United Kingdom has been reported as 7, 1.66, and 1.4 per 100,000 persons per year and as <1 in the predominantly Asian country Korea.<sup>8,11,13,33</sup> Greek and Korean studies found a majority of SN patients to be Fitzpatrick Type III or greater.<sup>9,11,17</sup> Overall the currently available data suggests Spitz neoplasms are likely more common in Caucasians, but the subject has not been sufficiently studied to form a definitive conclusion on this matter.

#### 4.1 | Exposures

No environmental exposures in the survey yielded a correlation with Spitz neoplasm development, including age of residence, smoking exposure, air quality, pesticide use, sunburns, time spent outdoors, CT imaging, and immunosuppression via chemotherapy, radiation therapy, or transplant. Age of residence, smoking exposure, air quality, pesticide use, and immunosuppression have not been widely studied in the literature. Two studies have investigated possible association of sunburns and Spitz development; however, our study yielded no statistical difference.<sup>9,17</sup> One study found no patients with tanning bed use, as was the case for our cohort.<sup>9</sup> The lack of a statistically significant association of Spitz tumors with UV exposure is consistent with the vast majority of Spitz neoplasms resulting from larger structural chromosomal rearrangements rather than somatic DNA mutations.

#### 4.2 | Medical history

Patients reported a personal cancer history in 4.7% of the Spitz cohort and 0.0% of the control cohort; however, this difference was not statistically significant ( $p=.16$ ). Meta-analysis revealed no studies in which personal cancer history was associated with Spitz neoplasm development.<sup>9</sup>

#### 4.3 | Family history

Our data found no significant difference between control and Spitz patients regarding family cancer or melanoma history. A case series of six AST and SM patients found 50% had a family history of non-melanoma skin cancer, and a review found family melanoma history

to be associated with AST.<sup>16,25</sup> However, most studies demonstrate no association of family skin cancer history with Spitz neoplasms. Our study as well as most other investigators report no association of Spitz neoplasms with family history of DNS.<sup>9</sup> Both the Spitz and control survey groups reported a considerably higher rate of melanoma family history (26.4% and 32.8%) than what is to be expected in the general public; one meta-analysis showed 3.1% of control population patients to report a family history of melanoma.<sup>34</sup> We attribute this to the fact that patients with a family history of melanoma are more likely to attend a dermatology clinic.

Our survey and meta-analysis show no reproducible genetic or environmental risk factors for Spitz neoplasms, which are largely caused by structural rearrangements of chromosomes resulting in chimeric fusion proteins with constitutively activated tyrosine kinases. No significant differences were found in race, UV exposure, environmental hazards, or family history of DNS or melanoma between Spitz and control groups after Bonferroni correction for multiple hypothesis testing. If there is an environmental exposure related to Spitz neoplasm development, it is not likely a powerful connection and more cases are required to support it.

Limitations included small overall sample size, self-reported responses (especially relating to family medical history), and recall bias, which may have obscured possible associations with Spitz neoplasm development. A larger study may be needed to more definitively exclude some low-level associations that can only be identified in large multicenter studies. Additionally, controls were obtained from pediatric dermatology clinic, a population that includes a greater proportion of patients with personal and family history of skin conditions, including melanoma and other genetically linked disorders.

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#### CONFLICT OF INTEREST

Dr. Gerami has served as a consultant for DermTech Inc. and Castle Biosciences and has received honoraria for this. All other authors report no relevant conflicts of interest.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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