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RESEARCH ARTICLE

Association of Non-Melanoma Skin Carcinomas and UV Exposure with Exfoliation Syndrome in Utah

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ABSTRACT

Background: Prior data suggest an association between non-melanoma skin cancer, i.e., basal and squamous cell cancers most often located in areas of sun exposure, and pseudoexfoliation syndrome. This study aimed to evaluate the association between these conditions and UV exposure through a detailed questionnaire in a large and robust Utah population.

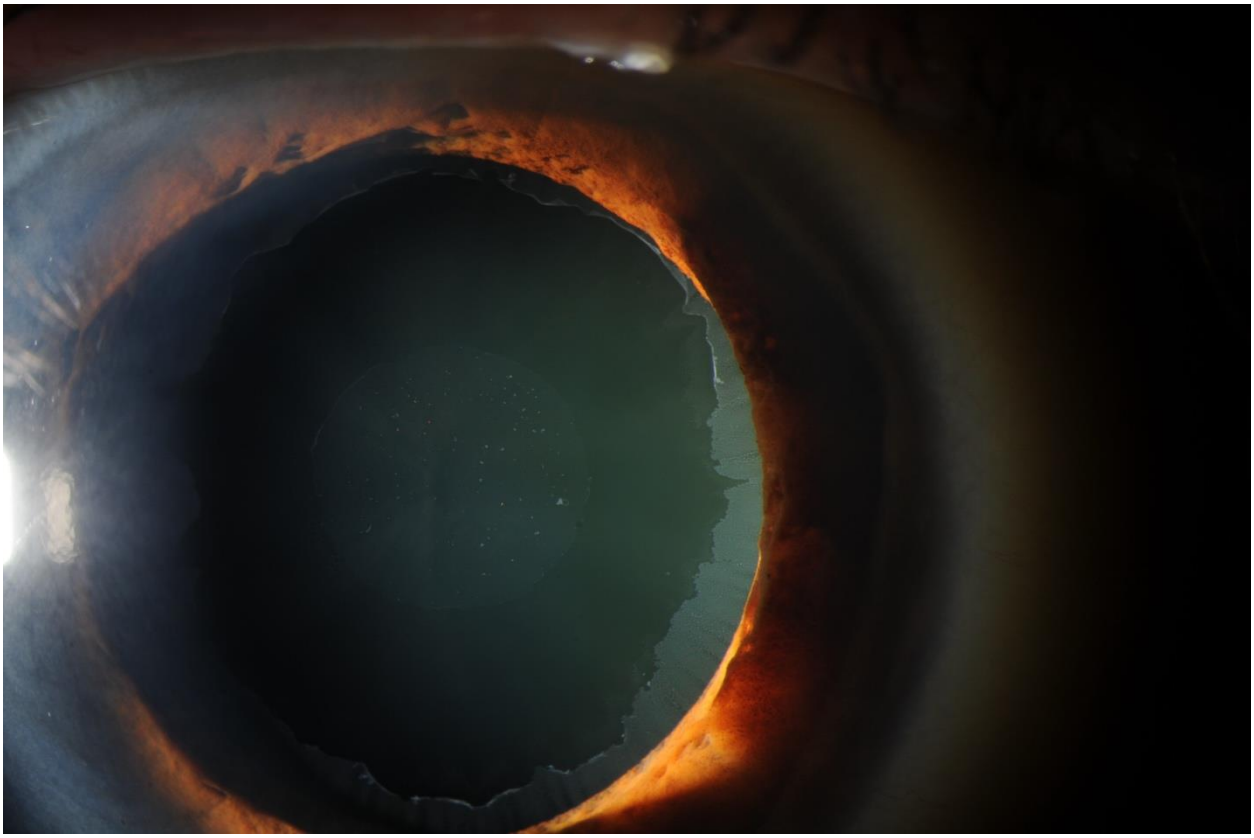
Methods: The two arms of this study are a population-based study (evaluated via chart review) and a UV exposure study (evaluated via a questionnaire). Participants answered a questionnaire designed to assess lifelong UV exposure, including leisure and occupational sun exposure, likelihood to tan or burn in early life, eye and hair color, smoking behavior, vitamin D deficiency, skin cancer history, alcohol consumption, and caffeine intake.

Conclusion: Descriptive findings suggest UV exposure over an adult's lifespan may associate with a higher risk of non-melanoma skin cancer in Utah exfoliation patients vs. unaffected individuals. Patients with exfoliation glaucoma reside at higher elevations than non-glaucoma patients.

Introduction

Exfoliation syndrome (XFS), first discovered in 1917 in a Finnish population, is a complex, inherited systemic disorder characterized by abnormal accumulation of extracellular matrix material (ECM) in the eye, heart, brain, lungs, and skin.[1-8] Deposition of fibrillar ECM debris, or exfoliation material (XFM), within anterior segment structures of the eye is the manifestation of clinically diagnosed XFS (see Figure 1), which is the most common recognizable cause of open-angle glaucoma worldwide.[9] XFS is rarely observed below age 50 and the prevalence increases significantly with age.[10] Patients with XFS are at high risk of developing exfoliation glaucoma (XFG), a particularly aggressive form of glaucoma, as well as more advanced and rapid cataract formation yet the contributing factors are not well identified.[11] XFS is an important preoperative consideration given that cataract surgery in XFS can carry a higher risk of intraoperative and postoperative complications given the laxity of the lens.[12,13]

Figure 1. The anterior segment of an eye with XFS.



Skin is a non-ocular tissue in which XFM deposits accumulate, and XFS has been shown to be associated with ultraviolet (UV) damage.[14,15] Non-melanoma skin cancers (NMSC; i.e., basal and squamous cell) are also caused by UV exposure and may be a

common insult linking these conditions hence the hypothesis behind this investigation. Genetic risk factors have been associated with XFS and In particular lysyl oxidase like-1 (LOXL1 genetic variants, a key enzyme in ECM deposition and repair.[16-20] Environmental and epigenetic factors have recently been hypothesized to increase XFS risk, such as higher latitude, altitude, and ocular UV exposure[21-24] previously assessed with a questionnaire in Massachusetts and Israel.[15] A questionnaire assessing XFS and NMSC in New York patients showed that craniocervical NMSC was associated with XFS/XFG.[25] Surveys of patients in other geographic locations are useful to validate these findings.

Prior studies suggested that the development of XFS is influenced by UV exposure. Identifying these environmental influencers and associations in a unique population would further support this hypothesis. This study aimed to evaluate the association between UV exposure, an environmental and genetic expression influencer, and the development of XFS in a unique, large population by determining the association of NMSC with XFS, through a detailed questionnaire about UV exposure in a subset of this population.

Methods

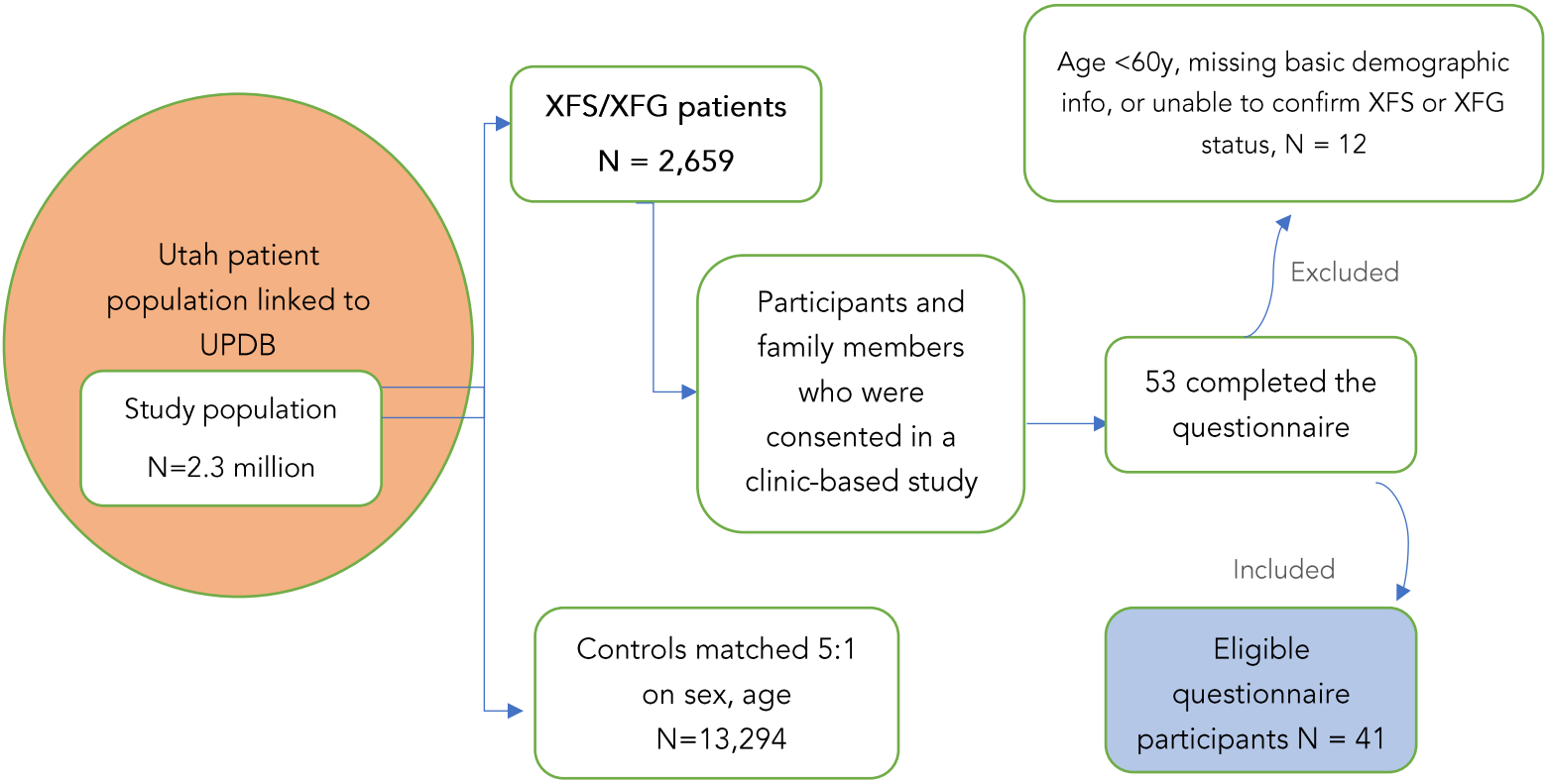
Population-based study. The Utah Population Database (UPDB) contains decades of statewide vital records linked with the electronic medical records of most individuals in Utah, as described in detail.[26] A retrospective cohort study design was used to examine NMSC in 2,653 XFS/XFG patients, and 5:1 population controls individually matched on sex and age were identified in UPDB records (Figure 1). Malignant melanoma and NMSC were obtained from a comprehensive statewide cancer registry, the Utah Cancer Registry (UCR), from 1966-2017. The UCR is annually record-linked to individuals contained within the UPDB, a key feature of this unique database. Patients diagnosed with XFS/XFG and prevalent diagnoses of NMSC in patients and controls (in situ basal and squamous cell neoplasia) were obtained from International Classification of Diseases (ICD) version 9 and 10 codes (Table 1, see appendix) in records from 1996-2017 of University of Utah Health (UHealth). UHealth is a comprehensive provider of healthcare services in hospitals and clinics throughout Utah and is the largest provider of eye care in the state. Diagnoses in clinical records of UHealth were obtained and linked to the UPDB as described.[27]

Table 1. ICD codes for XFS/XFG and non-melanoma skin cancers.

ICD9	ICD10 Code(s)	Diagnosis of XFS/XFG
365.52	H40.14	Pseudoexfoliation glaucoma
366.11	H25.89	Pseudoexfoliation of lens capsule
ICD9	ICD10 Code(s)	Diagnosis of NMSC
173.00	C44.00	Unspecified carcinoma of the lip
173.01	C44.01	Basal cell carcinoma of the lip
173.02	C44.02	Squamous cell carcinoma of the lip
173.10	C44.101, C44.102,	Unspecified carcinoma of the eyelid
173.11	C44.111, C44.112,	Basal cell carcinoma of the eyelid
173.12	C44.121, C44.122,	Squamous cell carcinoma of the eyelid
173.20	C44.201, C44.202,	Unspecified carcinoma of the ear
173.21	C44.211, C44.212,	Basal cell carcinoma of the ear
173.22	C44.221, C44.222,	Squamous cell carcinoma of the ear
173.30	C44.300, C44.301,	Unspecified carcinoma of the face
173.31	C44.310, C44.311,	Basal cell carcinoma of the face
173.32	C44.320, C44.321,	Squamous cell carcinoma of the face
173.40	C44.40	Unspecified carcinoma of the neck
173.41	C44.41	Basal cell carcinoma of the neck
173.42	C44.42	Squamous cell carcinoma of the neck
173.50	C44.500, C44.501,	Unspecified carcinoma of the trunk
173.51	C44.510, C44.511,	Basal cell carcinoma of the trunk
173.52	C44.520, C44.521,	Squamous cell carcinoma of the trunk
173.60	C44.601, C44.602,	Unspecified carcinoma of the upper limb incl.
173.61	C44.611, C44.612,	Basal cell carcinoma of the upper limb incl.
173.62	C44.621, C44.622,	Squamous cell carcinoma of the upper limb incl.
173.70	C44.701, C44.702,	Unspecified carcinoma of the lower limb incl. hip
173.71	C44.711, C44.712,	Basal cell carcinoma of the lower limb incl. hip
173.72	C44.721, C44.722,	Squamous cell carcinoma of the lower limb incl. hip
173.80	C44.80	Unspecified carcinoma, other specified site
173.81	C44.81	Basal cell carcinoma, other specified site
173.82	C44.82	Squamous cell carcinoma, other specified site
173.90	C44.90	Unspecified carcinoma, unspecified site
173.91	C44.91	Basal cell carcinoma, unspecified site
173.92	C44.92	Squamous cell carcinoma, unspecified site

ABBREVIATIONS: XFS - Exfoliation Syndrome; XFG - Exfoliation Glaucoma; NMSC - Non-melanoma Skin Cancer

Figure 2. Study population and study subject selection.



Statistical methods, population-based study. A chi-square test of association was used to compare the characteristics of subjects in the XFS/XFG case patient and matched control cohorts. Conditional logistic regression was used to estimate the risk of NMSC and melanoma in XFS/XFG patients compared with controls while controlling for sex and age from individual matching and adjusting for race and ethnicity. In our survey of all XFS/XFG patients identified in electronic medical records and random unaffected random controls matched 5:1 as described above, the study size was well-powered (>95%) to detect a statistical difference in NMSC outcomes between groups.

UV exposure study. Patients in the XFS/XFG population cohort and their family members who subsequently were recruited and enrolled in a clinic-based study and who consented to be contacted (N=151) were sent a questionnaire assessing sun exposure history, medical history, and social habits. The presence of XFG was determined through ICD coding and chart review to confirm diagnoses of the presence of XFM and an elevated IOP. Altitude was determined from the location of residence at the time of the survey found in the electronic medical record for each patient or family member. Our questionnaire is similar to that of Huang et al.,[25] yet differs in that we added the

following: UV exposure throughout one's lifetime, smoking and alcohol consumption history, vitamin D supplementation, caffeine intake, and the geographic location given this study is at a much higher elevation. The questionnaire distributed is included as a supplemental document in the appendix.

Of 53 respondents, 41 patients were eligible for analysis (Figure 1). Fifty-three patients of Moran Eye Center clinics completed the questionnaire identified as non-Hispanic and white. Twelve respondents were excluded for: age at diagnosis (under 60y); missing birth date and basic demographic information; and unavailable electronic health records (EPIC system) to confirm absence or presence of XFS/XFG and medical history. The questionnaire obtained usual UV exposure (leisure, occupational) at: 1) age <20y, 2) ages 21-64y, and 3) ≥65y. Participants were asked about time spent outdoors (hours/day, days/week in winter (November-April) and summer (May-October), including activities such as skiing and swimming.

Statistical methods, UV exposure study. Responses were converted to total hours of sun exposure and categorized within age groups: 0-25th percentile, low exposure; 26th-75th percentile, intermediate exposure; >75th percentile, high exposure. Smoking and alcohol history, vitamin D supplementation, skin cancer history, and caffeine intake were also obtained. A Fisher's exact test was used to examine differences between XFS/XFG and unaffected subjects. A t-test with log transformation was used to assess differences in geometric mean elevation. Sample size was limited, with estimated power of 25% to detect a statistically significant difference of 20% between patients and unaffected subjects.

Results

Population-based study. Based on a chi-square test of association, case patients and controls did not differ significantly in sex and age (matching variables); however, XFS/XFG patients and controls differed somewhat for race and ethnicity (Table 2), although both cohorts are majority white and non-Hispanic similar to the Utah population. Among the 2,659 XFS/XFG patients, 227 (8.5%) had one or more diagnoses of NMSC. In comparison, 829 (6.2%) of 5:1 controls had an NMSC diagnosis (Table 2). From the logistic model that accounted for individual matching on sex and age, the risk of NMSC was approximately 50% higher in XFS/XFG than in controls (Odds Ratio 1.46, 95% CI 1.25-1.71; $p<0.0001$), after adjustment for race and ethnicity. Conversely, there was no association between melanoma in XFS/XFG compared with controls.

Table 2. Skin cancers in XFS/XFG patients compared with 5:1 controls.

	Controls		XFS/XFG		
Characteristic	N	col%	N	col%	P_{chisq}
Total patients	13,294	100.0	2,659	100.0	
Men	4,379	32.9	876	32.9	
Women	8,915	67.1	1,783	67.1	*>0.99*
Age at case diagnosis					
Mean (±s.d.)	74.2	10.8	74.2	10.8	*>0.99*
Race					
Non-white	865	6.5	307	11.5	
White	12,429	93.5	2,352	88.5	*<0.0001*
Ethnicity					
Hispanic	1,033	7.8	172	6.5	
Not Hispanic	12,259	92.2	2,487	93.5	*0.02*
NMSC (Basal cell, squamous cell, unspecified if basal or squamous)					
Diagnosed	829	6.2	227	8.5	
Not diagnosed	12,465	93.8	2,432	91.5	*<0.0001*
Basal cell					
Diagnosed	520	3.9	147	5.5	
Not diagnosed	12,774	96.1	2,512	94.5	*0.0001*
Squamous cell					
Diagnosed	493	3.7	138	5.2	
Not diagnosed	12,801	96.3	2,521	94.8	*0.0003*
Malignant melanoma					
Diagnosed	375	2.8	69	2.6	
Not diagnosed	12,919	97.2	2,590	97.4	*0.52*

ABBREVIATIONS: XFS - Exfoliation Syndrome; XFG - Exfoliation Glaucoma; NMSC - Non-melanoma Skin Cancer, in-situ and malignant (reportable to the Utah Cancer Registry).

UV exposure study. All 41 eligible survey respondents were ages 60y and older and identified as non-Hispanic and white. Those with XFS/XFG, XFG only (XFS who developed glaucoma), and unaffected individuals did not differ by sex, age, or history of NMSC (Table 3, Fisher's exact test). Lifestyle factors did not differ (smoking, alcohol, caffeine consumption; data not shown). A higher proportion of those who developed XFG resided at higher elevations (>5500 ft; Table 3). Geometric mean residence elevation was higher for XFG specifically, although the difference was not statistically significant (P_{XFG}=0.10; Table 3, t-test with log transformation). We observed XFS/XFG patients were more likely to report high sun exposure between ages 21-64y than unaffected participants ($P_{XFS/XFG}$=0.05, P_{XFG}=0.03; Table 3, Fisher's exact text). Sun exposure during pre-adulthood or retirement-age years was not associated.

Table 3. Characteristics of questionnaire respondents.

	XFS/XFG		XFG only		Unaffected			
	N	%	N	%	N	Col%	$P_{XFS/XFG}$	P_{XFG}
Total	31		23		10			
Men	11	35.5	8	34.8	4	40.0		
Women	20	64.5	15	65.2	6	60.0	*1.00*	*1.00*
Age at response								
60-69	3	9.7	2	8.7	4	40.0		
70-79	15	48.4	11	47.8	3	30.0		
80 & older	13	41.9	10	43.5	3	30.0	*0.11*	*0.12*
NMSC								
History	7	22.6	6	26.1	3	30.0		
No history	24	77.4	17	73.9	7	70.0	*0.68*	*1.00*
Residence elevation (feet):								
Geometric mean (c.v.)	4,502	0.54	4,819	0.16	2,752	3.4	*0.13*	*0.10*
<4000 ft	1	3.2	0	0.0	1	10.0		
4000-5500 ft	22	71.0	18	78.3	8	80.0		
>5500 ft	8	25.8	5	21.7	1	10.0	*0.41*	*0.30*
Sun exposure total hours, percentiles (%):								
Age 20 and younger								
0 to 25th%	7	22.6	6	26.1	2	20.0		
26th to 75th%	16	51.6	10	43.5	5	50.0		
>75th%	8	25.8	7	30.4	3	30.0	*1.00*	*1.00*
Age 21y to 64y								
0 to 25th%	9	29.0	7	30.4	1	10.0		
26th to 75th%	14	45.2	9	39.1	9	90.0		
>75th%	8	25.8	7	30.4	0	0.0	*0.05*	*0.03*
Age 65y and older								
0 to 25th%	7	22.6	5	21.7	4	40.0		
26th to 75th%	15	48.4	11	47.8	5	50.0		
>75th%	9	29.0	7	30.4	1	10.0	*0.46*	*0.44*

Abbreviations: XFS - Exfoliation Syndrome; XFG - Exfoliation Glaucoma; NMSC - Non-melanoma Skin Cancer; C.V. - Coefficient of Variation. Note: Fisher's exact test, categorical data; for t-test log transformation, continuous data.

Discussion

Tissue insult secondary to UV exposure is a possible shared pathogenesis between XFS and NMSC via triggering molecular pathways that in turn perform and result in abnormal extracellular matrix accumulation.[28] Our questionnaire sought to assess UV exposure over participants'

lifetimes, made uniquely possible by the decades of vital and other records contained in the UPDB, a unique feature while still being complementary to previous questionnaires.[15,25] Our cohort findings are consistent with prior studies using NMSC as a proxy for UV exposure and associated with XFS.[24,25] An elevated rate of NMSC in XFS/XFG versus non-XFS patients is not well understood, but it is possible that UV exposure may be a contributing risk factor to both pathologies. Although we did not observe higher rates of self-reported NMSC in our limited survey of respondents, findings suggest that greater UV exposure over the adult life course may be associated with a higher risk of development of XFG in XFS patients.

The environmental risk factor of increased UV exposure could contribute to XFS rates in rural communities and those with outdoor occupations.[21] Vojniković et al. observed XFS was found in 110 of the 480 fishermen or agriculturalists but none of the 60 urban residents in the Northern Adriatic Sea.[29] A previous study in southern India discovered people who worked outdoors had an elevated odds ratio of XFS.[30] However, a low XFS prevalence was noted in the Innuits of Greenland and Peruvian people of Lake Titicaca (4000m, sunny, low humidity).[31,32] We hypothesized our mixed population of individuals residing in urban Salt Lake City and also rural and farming communities across the state, would have elevated rates of XFS due to ample UV exposure and possibly outdoor occupations commonly associated with rural, farming communities. There are likely other environmental factors contributing to XFS and NMSC rates in these populations.

Although XFS was initially identified primarily as an inherited disease in individuals of Scandinavian descent, it has been hypothesized that various environmental factors increase the risk of XFS.[1,21] XFS has been found in those at higher altitudes, latitudes further from the equator and epigenetics as UV can contribute to epigenetic changes (i.e., DNA methylation).[21,22,33]

Our population lives at a relatively higher elevation of roughly 4,500 ft in surrounding regions of the Salt Lake Valley. Two previous studies found XFS to be more prevalent at higher altitudes[34,35], but Stein found higher altitudes with increased sunny days had a decreased hazard ratio.[23] They also reported greater sunshine exposure and lower ambient temperatures in summer and winter increased the likelihood of XFS.[23] Kang and Stein found increased latitudes in the United States may contribute to elevated XFS risk and Stein noted risk was the same in nonwhite and white beneficiaries, suggesting environmental factors may be contributing more than genetics in their study population.[23,36] Smoking and caffeine have also been associated with DNA methylation, thus possibly conferring the risk of disease.[33] An increased risk of XFS and NMSC with farming occupation, smoking, and caffeine intake in XFS/XFG respondents and those unaffected was not observed, possibly due to bias inherent in a small sample. Elucidation of environmental factors linked to XFS could

lead to primary prevention measures for these conditions.

Our retrospective population-based study of 2,659 XFS/XFG patients and 5:1 controls is one of the largest to date to examine the association of NMSC and XFS/XFG in a statewide population. Further, to our knowledge this is the first study of its kind to be conducted in Utah. Clinicians of the UHealth Moran Eye Center and satellite clinics are experts in diagnosing XFS via dilated eye exams, and our patient population was confirmed through chart reviews to minimize misclassification. In contrast, the UV exposure study with the questionnaire represented a convenience sample of a small subset of enrolled clinic patients and family members within the larger study, and respondents self-selected participation. Potential selection bias and limited sample size limit the generalizability of results to other populations. Additionally, recall bias may play a role as most advanced age patients would have difficulty recollecting details or specifics from their earlier years. A consideration for generalizability is the population majority in Utah self-identifies as non-Hispanic white with a predominant ancestry from northern Europe.

Conclusion

Consistent with prior studies, Utah respondents with XFS/XFG appeared more likely to reside at higher elevations and may have increased UV exposure in their young adult life. Identifying differences in UV exposure and non-UV lifestyle factors, as well as the development of NMSC among XFS, XFS with XFG, and unaffected individuals, should be pursued in larger population-based studies.

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Conflict of Interest Statement
The authors have no conflicts of interest to declare.

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Questionnaire:

Form 1

Record ID _____

Questionnaire assigned number _____

1. During the summer and "shoulder" months of May through October estimate the usual number of days each week spent outdoors between 10 am and 4 pm

- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6
- ○ 7
- ○ I did not spend time outdoors (skip to question #5)
- ○ I don't know (skip to question #5)

2. How many hours each day did you usually spend outdoors between 10am and 4pm during summer (May-October)?

_____hours each day

- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6

3. When you were outdoors in May-October, how often did you wear UV eye protection such as: sunglasses (including clip-on), a hat with a brim, or a visor?	○ never/rarely (0-10% of the time) ○ sometimes (>10-40%) ○ about half the time (>40-60%) ○ most of the time (>60-85%) ○ all/nearly all of the time (>85-100%)
4. When you were outdoors in summer (May-October), how many days per week on average did you spend 2 or more hours in an activity on or near a body of water (such as an ocean, lake or pond, or a swimming pool?)	○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ I did not spend time near water for 2 or more hours in a day ○ I don't know
5. During the winter and "shoulder" months of November through April, estimate the usual number of days each week spent outdoors between 10 am and 4 pm): _____days	○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ I did not spend time outdoors (skip to question #9) ○ I don't know (skip to question #9)
6. How many hours each day did you usually spend outdoors between 10 am to 4 pm during winter (November-April)?	○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6

7. When you were outdoors in November-April, how often did you wear UV eye protection such as: sunglasses (including clip-on), ski goggles, a hat with a brim, or a visor?	◯ never/rarely (0-10% of the time) ◯ sometimes (>10-40%) ◯ about half the time (>40-60%) ◯ most of the time (>60-85%) ◯ all/nearly all of the time (>85-100%)
8. When you were outdoors in winter (November-April), how many days per week on average did you spend 2 or more hours in an activity on or near snow or ice (such as skiing, ski lessons (teacher/student), sledding, ice skating or shoveling snow)?	◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ I did not spend time near snow or ice for 2 or more hours in a day ◯ I don't know
9. During the summer and "shoulder" months May through October, estimate the usual number of days each week spent outdoors between 10 am and 4 pm:	◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ I did not spend time outdoors (skip to question #13) ◯ I don't know
10. How many hours each day did you usually spend outdoors between 10 am and 4 pm during summer (May-October)?	◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6

11. When you were outdoors in May-October, how often did you wear UV eye protection such as: sunglasses (including clip-on), a hat with a brim, or a visor?	○ never/rarely (0-10% of the time) ○ sometimes (>10-40%) ○ about half the time (>40-60%) ○ most of the time (>60-85%) ○ all/nearly all of the time (>85-100%)
12. When you were outdoors in summer (May-October), how many days per week on average did you spend 2 or more hours in an activity on or near a body of water (such as an ocean, lake or pond, or a swimming pool?).	○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ I did not spend time near water for 2 or more hours in a day ○ I don't know
13. During the winter and "shoulder" months of November through April, estimate the usual number of days each week spent outdoors between 10 am and 4 pm):	○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ I did not spend time outdoors (skip to question #17) ○ I don't know (skip to question #17)
14. How many hours each day did you usually spend outdoors between 10 am and 4 pm during winter (November-April)?	○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6

15. When you were outdoors in November-April, how often did you wear UV eye protection such as: sunglasses (including clip-on), ski goggles, a hat with a brim, or a visor?

- ○ never or rarely (0-10% of the time)
- ○ sometimes (>10-40%)
- ○ about half the time (>40-60%)
- ○ most of the time (>60-80%)
- ○ all/nearly all of the time (>85-100%)?
- ○ never or rarely (0-10% of the time)

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16. When you were outdoors in winter (November-April), how many days per week on average did you spend 2 or more hours in an activity on or near snow or ice (such as skiing, ski lessons (teacher/student), sledding, ice skating or shoveling snow)?

- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6
- ○ 7
- ○ I did not spend time near water for 2 or more hours in a day
- ○ I don't know

If you are age 65 or older, please estimate for leisure activities not related to a job (if you are younger than 65, skip to question #25):

17. During the summer and "shoulder" months of May through October, estimate the usual number of days each week spent outdoors between 10 am and 4 pm:

- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6
- ○ 7
- ○ I did not spend time outdoors (skip to question #25)
- ○ I don't know

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18. How many hours each day did you usually spend outdoors between 10 am to 4 pm during summer (May-October)?

- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6

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19. When you were outdoors in May-October, how often did you wear UV eye protection such as: sunglasses (including clip-on), a hat with a brim, or a visor?

- ○ never or rarely (0-10% of the time)
- ○ sometimes (>10-40%)
- ○ about half the time (>40-60%)
- ○ most of the time (>60-80%)
- ○ all/nearly all of the time (>85-100%)?

20. When you were outdoors in summer (May-October), how many days per week on average did you spend 2 or more hours in an activity on or near a body of water (such as an ocean, lake or pond, or a swimming pool?)

- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6
- ○ 7
- ○ I did not spend time near water for 2 or more hours in a day
- ○ I don't know

21. During the winter and "shoulder" months of November through April, estimate the usual number of days each week spent outdoors between 10 am and 4 pm):

- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6
- ○ 7
- ○ I did not spend time outdoors (skip to question #25)
- ○ I don't know (skip to question #25)

22. How many hours each day did you usually spend outdoors between 10 am and 4 pm during winter (November-April)?

- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6

23. When you were outdoors in November-April, how often did you wear UV eye protection such as: sunglasses (including clip-on), ski goggles, a hat with a brim, or a visor?	○ never/rarely (0-10% of the time) ○ sometimes (>10-40%) ○ about half the time (>40-60%) ○ most of the time (>60-85%) ○ all/nearly all of the time (>85-100%)
24. When you were outdoors in winter (November-April), how many days per week on average did you spend 2 or more hours in an activity on or near snow or ice (such as skiing, ski lessons (teacher/student), sledding, ice skating or shoveling snow)?	○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ I did not spend time near water for 2 or more hours in a day ○ I don't know
General Questions	
25. Did you ever work as a farmer, construction worker, truck/tractor driver, or in a job where you spent most of the day working outdoors?	○ yes, worked mostly outdoors ○ no, did not work mostly outdoors (skip to question #28) ○ don't know (skip to question#28)
26. What was your occupation when you worked outdoors?	_____
How many years total did you work at this job?	_____
27. How many hours in an average day did you work outdoors?	○ 8 or more hours ○ 6-7 hours ○ 4-5 hours ○ less than 4 hours

28. Have you mostly been the driver or the passenger when in a car between the ages of 16-39 years old? (did you drive a tractor?)	○ Driver ○ Passenger ○ not sure ○ N/A
28. Have you mostly been the driver or the passenger when in a car between the ages of 40-65 years old? (did you drive a tractor?)	○ Driver ○ Passenger ○ not sure ○ N/A
28. Have you mostly been the driver or the passenger when in a car between the ages of 65 and older? (did you drive a tractor?)	○ Driver ○ Passenger ○ not sure ○ N/A
29. Do you currently smoke cigarettes or regularly use any tobacco products (pipe, cigars, chewing tobacco)?	○ Yes ○ No, former smoker (quit) ○ No, never smoked or used tobacco (if no, skip to question #32)
30. How many packs of cigarettes do you (or, if former smoker, did you) usually smoke each day?	○ less than a ½ pack per day ○ ½ to less than 1 pack per day ○ 1 to 1½ packs per day ○ 2 to 2-1/2 packs per day ○ 3 or more packs each day ○ I smoke (or used to smoke, if quit) pipes, cigars, or used chewing tobacco
31. How many years total have you smoked cigarettes, pipes, cigars, or used chewing tobacco (if you started and stopped, please include only the total number of years that you smoked or used tobacco)	_____

32. Have you ever been diagnosed with a Vitamin D deficiency?

- ○ Yes, I have been diagnosed with Vitamin D deficiency
- ○ No

33. Do you regularly take supplemental Vitamin D including: drinking Vitamin D fortified milk, taking a multivitamin, or taking vitamin D supplement with or without calcium?

- ○ Yes, I have been diagnosed with Vitamin D deficiency
- ○ No, (if no, skip to question #35)

34. If yes, for how long have you been taking supplemental Vitamin D in milk, multivitamins, or supplement pills / chews? (how many years?)

_____

35. At what age was your first sunburn?

- ○ Age 10 or younger
- ○ Age 11 to age 20 Age 11 to age 20
- ○ Age 21 to age 30
- ○ Age 31 to age 40
- ○ over age 40
- ○ never had a sunburn (skip to question #36)

35. Do you tend to tan or burn when in the sun? If you do burn, would you say you had over your lifetime: a few sunburns (< 5), many (5-15), or an excessive number (more than 15)?

- ☐ I tend to tan
- ☐ I tend to burn
- ☐ I don't know
- ☐ Few sunburns(< 5)
- ☐ Many (5-15)
- ☐ Excessive (>15)

36. While growing up, what was your natural hair color? (for example, blonde, brown, black, or auburn/red)?

_____

37. What is your eye color (for example, brown, blue, green, hazel)?	
38. Have you ever had skin cancer? If yes, what type of skin cancer? If yes, where was the skin cancer? (skin cancer, type, location)	
39. Did you ever regularly drink alcoholic beverages (1 or more times a month on average)? Alcoholic beverages include beer, wine, or distilled spirits (such as vodka or whiskey)?	○ Yes ○ No (if no, survey over)
40. What age were you when you started drinking alcoholic beverages?	_____
41. What age were you when you stopped drinking alcoholic beverages? (0 means still drinking)	_____
42. On average how many drinks* per week did you or do you consume?	○ occasionally (< 1 to 2 drinks each week) ○ 3 to < 7 drinks (about 1-2 drinks every other day) ○ 7 to 14 drinks (1-2 drinks per day) ○ more than 14 drinks (more than 2 drinks per day) ○ none
Caffeine intake?	○ Yes ○ No

Number cups of tea per day _____

Number cups of coffee per day _____