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Lifetime UV exposure and Lentigo Maligna Melanoma

E. Linos¹, W.Q. Li^{2,3}, J. Han^{4,5,6}, T. Li^{2,3}, E. Cho^{2,3,4}, and A.A. Qureshi^{2,3,4}

¹Department of Dermatology, University of California San Francisco

²Department of Dermatology, Warren Alpert Medical School

³Department of Epidemiology, School of Public Health, Brown University, Providence, RI, United States

⁴Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

⁵Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University, Indianapolis, IN, United States

⁶Melvin and Bren Simon Cancer Center, Indiana University, Indianapolis, IN, United States

Although ultraviolet light is considered a key factor in the etiology of malignant melanoma (MM), the relationship between sunlight and MM is complex.^{1,2} Intermittent exposure and sunburns are far more predictive of melanoma than chronic exposure, and melanoma can arise in non-sun exposed sites.³ Furthermore, retrospective studies have shown that outdoor workers exposed to sunlight chronically are not at higher risk of melanoma compared with indoor workers living at the same latitude.^{2,4} One possible explanation is that different types of malignant melanoma arise from distinct etiologic pathways. Initial evidence at the genetic level supports this theory; BRAF and N-RAS mutations are more common in MM found in intermittently exposed skin compared to chronically sun-damaged skin.^{5,6} Lentigo maligna melanoma (LMM) is a subtype of melanoma arising in chronically sun-exposed skin, commonly on the face, and frequently diagnosed in older patients.^{7–10} Mutations in BRAF are rare in LMM, compared to melanomas occurring on skin subject to intermittent sun exposure.^{5,6} Thus, it is possible that LMM arises from a distinct environmental and genetic pathway compared to other types of cutaneous melanoma.

The goal of this study was to examine the effect of lifetime UV exposure on incident lentigo maligna melanoma prospectively.

Corresponding author: Eleni Linos, MD, DrPH, Assistant Professor, Department of Dermatology, 2340 Sutter Street, Room N413, San Francisco, CA 94143-0808, Phone: 415-476-9755; Fax: 415-476-6751; eleni.linios@ucsf.edu.

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Author Contributions: Dr Qureshi had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Qureshi, Linos *Acquisition, analysis, and interpretation of data:* Drafting of the manuscript: Linos, Li, Han, Cho, Qureshi. *Critical revision of the manuscript for important intellectual content:* Linos, Li, Han, Cho, Qureshi *Statistical analysis:* Li, Linos, Han *Obtained funding:* Qureshi *Administrative, technical, or material support:* Qureshi *Study supervision:* Qureshi

METHODS

The Nurses' Health Study (NHS) and the Health Professionals Follow up Study (HPFS) are ongoing, prospective cohort studies including 121,700 female nurses, and 51,529 male health professionals followed biennially.⁷ In 1992, participants in both cohorts were asked about location of residence (US state), at birth and at 15 and 30 years of age. The erythematous UV index (referred to as the UV index) is a method to estimate UV radiation reaching the earth's surface. US states were divided into the following 3 UV index groups: 5 or less (low UV index), 6 (medium UV index); and 7 or more (high UV index). Every two years, participants were asked to report any new diagnosis of cancer, including malignant melanoma. Diagnoses were confirmed by physicians using histopathology reports. Accumulation of follow-up time ceased at the first report of melanoma, death, or the return of the 2010 questionnaires, whichever came earliest. Cox proportional hazards models were run for univariate analyses, age-adjusted, and multivariate analyses.⁸ Covariates used in multivariate models included: hair color, ability to tan, number of blistering sunburns, skin susceptibility to burn, number of moles, family history of melanoma, history of prior non-melanoma skin cancer, and self-reported, systemic cancers. To evaluate melanoma risk of women who lived in areas of high or low UV index throughout their life, we performed a sub-analysis of women who reported living in areas of high, low, or medium UV index at all 3 time points: birth, at age 15, and at 30 years of age. Reference group was low UV index for each time period.

RESULTS

A total of 2414 incident cases of malignant melanoma, including 381 lentigo maligna melanoma were diagnosed among cohort participants and 3,443,621 person years of follow up. The majority of LMM were on head and neck (53%) compared to 17% of non-LMM. Participants who were born and stayed in areas of high UV index throughout their lifetime, were at higher risk of LMM compared to those who stayed at low UV index states (RR=1.51, 95% CI 0.98–2.32, p=0.03). Higher risks of LMM were noted when comparing high UV index to low UV index at each life-time point (birth, age 15, and age 30), but these did not reach statistical significance. UV index was not significantly related to other melanoma subtypes at any time point in this analysis.

DISCUSSION

In this large prospective study of over 170,000 men and women, we found a significant association between high lifetime UV exposure and lentigo maligna melanoma, but not other melanoma subtypes. Associations for LMM were strongest among those who stayed at high UV residence from birth through adulthood, suggesting a dose-response effect. These findings suggest that UV exposure may be an independent risk factor for LMM, with important implications for both our understanding of disease etiology and prevention messages. In the same cohort, the relative risk of lifetime exposure to a high UV index was 2.07 for SCC and 1.30 for BCC,¹ compared to RR=1.01 for other types of melanoma which are not considered to be linked to chronic sunlight exposure.

Lentigo maligna melanoma is much more common on the head and neck area compared to other body sites. In fact, almost 50% of melanomas of the head and neck are LMM type, compared to 2% on other anatomic sites. Prior studies have described the unique features of head and neck melanomas, although these differences are probably more due to histologic subtype rather than pure anatomic differences.¹⁰ Our findings are consistent with the growing body of genetic evidence on the heterogeneity of melanoma subtypes.^{5,6}

In conclusion, our data suggests that the associations between melanoma and UV index may differ according to melanoma type with stronger associations for LMM compared to non-LMM. Our findings support the hypothesis that lentigo maligna melanoma may have a distinct etiology compared to other melanoma subtypes, and imply that chronic UV exposure may be an independent risk factor for LMM.

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What's already known about this topic?

Lentigo Maligna Melanoma typically occurs in sun exposed areas on the head and neck.

What does this study add?

Our data from two large prospective studies including over 2,000 cases of melanoma suggests that the associations between melanoma and chronic UV exposure may differ according to melanoma type with stronger associations for lentigo maligna compared to other melanoma subtypes.

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Table 1

Multivariate relative risk (95% confidence interval) of lentigo maligna melanoma and non-lentigo maligna melanoma in the combined data set of NHS and HPFS

		Lentigo maligna melanoma (N=382)			Non-lentigo maligna melanoma (N=2035)		
	Gender	Number of cases	Person-years	HR (95% CI)	Number of cases	Person-years	HR (95% CI)
	Female	221	2644064	1.00	1437	2644064	1.00
	Male	161	797647	1.51 (1.12– 2.05)	598	797647	1.25(1.09–1.44)
	<i>p</i> -trend			0.008			0.001
	UV index at birth						
	Low	79	878435	1.00	481	878435	1.00
	Medium	191	1540398	1.33(1.02,1.72)	1016	1540398	1.19(1.07,1.33)
	High	57	392643	1.23(0.87,1.74)	250	392643	1.02(0.87,1.94)
	<i>p</i> -trend			0.16			0.19
	UV index at age 15						
	Low	86	872193	1.00	488	872193	1.00
	Medium	179	1539870	1.14(0.88,1.47)	992	1539870	1.14(1.02,1.27)
	High	61	402185	1.17(0.84,1.65)	269	402185	1.04(0.90,1.22)
	<i>p</i> -trend			0.35			0.18
	UV index at age 30						
	Low	61	750803	1.00	423	750803	1.00
	Medium	182	1488848	1.52(1.13,2.03)	956	1488848	1.14(1.02,1.28)
	High	76	507583	1.50(1.07,2.11)	323	507583	1.01(0.87,1.17)
	<i>p</i> -trend			0.02			0.59
	Lifetime UV index						
	Low	45	591891	1.00	323	591891	1.00
	Medium	147	1198434	1.58(1.13, 2.21)	779	1198434	1.19(1.04,1.35)
	High	41	263328	1.51(0.98,2.32)	173	263328	1.03(0.85,1.25)
	<i>p</i> -trend			0.03			0.21

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Multivariate analyses were adjusted for age, gender, hair color, ability to tan, number of blistering sunburns, skin susceptibility to burn, number of moles, family history of melanoma, direct sun exposures at high school, at age 25–35, age 36–59 and age 60–65, history of prior non-melanoma skin cancer, and self-reported systemic cancers.^g

^g The reference group for each comparison is low UV index at the same time period as that comparison.