Published in final edited form as:

J Eur Acad Dermatol Venereol. 2019 July ; 33(7): 1268–1271. doi:10.1111/jdv.15348.

Gender differences, UV exposure, and risk of lentigo maligna in a nationwide healthcare population cohort study

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Abstract

Background: Our understanding of the relationship between ultraviolet radiation exposure and lentigo maligna (LM) has been largely derived from epidemiologic/clinical studies based on invasive melanoma. Recent studies have shown gender differences in melanocytic tumors incidence.

Objective: To examine the association of UV light with LM by gender remains unclear.

Methods: Two prospective cohort study (Nurses' Health Study [1980–2012]) and (Health-Professionals Follow-up Study [1986–2010]) were analyzed. All participants with LM or MIS, non-LM type were included in analysis. UV index at birth, age 15, and age 30 were calculated by gender. Lifetime UV flux was calculated. Hazard ratios (HRs) were calculated.

Results: 110,485 women from NHS and 41,015 men from HPFS were examined. 281 LM and 776 melanoma in situ (MIS), non-LM cases were reported. Risk of LM increased with increasing UV flux exposure in multivariate-adjusted models for men (p for trend=0.04), but not for women (p for trend=0.91).

Conclusions: UV flux may be associated with LM in men but not in women.

Introduction

Over the last decade, melanoma in situ (MIS) incidence has increased 9.5% per year, representing one of the fastest growing malignancies in the Surveillance, Epidemiology, and End Results (SEER) database.¹ The incidence of lentigo maligna (LM), considered the most common subtype of MIS, has similarly increased. Despite this trend, our understanding of LM is derived largely from epidemiologic and clinical studies that looked primarily at

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Conflicts of Interest: The authors declare no conflicts of interest.

invasive melanoma (MM). Few studies have solely evaluated the clinical epidemiology and risk factors of LM, representing a gap in our field's knowledge.

Understanding the epidemiology of LM is especially important because this tumor may have unique risk factors compared to other subtypes of MIS. Exposure to ultraviolet (UV) light is a key risk factor for development of melanoma. However, current studies on UV exposure patterns often do not differentiate LM from other subtypes of melanoma in their analyses.^{1,2}

In addition, some studies are showing that gender differences play a role in risk of MM, with positive associations of UV index and melanoma stronger in males than in females.³ Even when accounting for presumed gender-based behavioral differences, such as women being more likely to visit a doctor to have a lesion evaluated or working more often in indoor settings compared to men, women with MM are observed to have better prognosis.^{4–6} Therefore, biological gender differences may influence the epidemiology of LM as well.

As such, the association of UV light with LM by gender remains unclear. This study prospectively examined the effect of UV exposure on LM based on large nationwide cohorts of women and men.

Methods

This study examined data from 2 prospective cohorts (Nurses' Health Study (NHS) [1980–2012]) and (Health-Professionals Follow-up Study (HPFS) [1986–2010]). The NHS started in 1976 with a female cohort of 121,701 nurses ranging in age 30–55 years. The HPFS is a male cohort started in 1986 and comprises 51,529 health professionals ages 40–75 years. Information on disease history and lifestyle habits is obtained biennially by self-reported questionnaires for each cohort. The average response rate for each-year cycle of mailed questionnaires is more than 90%. Both NHS and HPFS participants biennially reported new diagnosis of skin cancer. If melanoma was reported, study physicians reviewed the participants' medical and pathological records to confirm the diagnosis. Only histopathologically confirmed cases of LM and MIS were included in the study.

All participants with histopathologically confirmed cases of LM or MIS, non-LM type identified during the follow-up were included for analysis. We examined the risk of LM or MIS, non-LM type associated with adulthood lifetime UV flux in men, women, and the combined population. UV flux represents radiant energy per unit area and measured in Robertson–Berger (RB) meter units, also known as sunburn units. It estimates UVB and part of UVA radiation (total range 290–330nm) reaching the earth's surface taking into account altitude, cloud cover, and latitude.⁷ UV radiation is monitored by a magnesium tungstate sensor and weighted according to an action spectrum that parallels that for skin erythema. An amount of 440 RB units may produce a typical sunburn reaction to untanned Caucasian skin. This amount of biologically effective radiation (relative to a wavelength of 297 nm) is referred to as the minimal erythema dose (MED) and is equivalent to $\sim 25\text{--}35 \text{ mJ cm}^{-2}$.

Compared to UV index, a UV dose estimate based on a single time point, UV flux more accurately reflects each participant's cumulative sun exposure, taking into account UV radiation levels based on residential history. Comparatively, information on UV index was

only available at specific time points, i.e. birth, age 15, age 30, and did not account for intervening time intervals when sun exposure could have differed.⁸ We therefore focused only on UV flux but not UV index variables in our current analyses.

Sun exposure characteristics have previously been reported and are also controlled for in multivariate analysis.⁹ Hazard ratios were calculated based on Cox proportional hazards regression models and the analyses were carried out by using SAS (version 9.2; Cary, NC). *P* values were 2-tailed with significance level at *P*<0.05.

Results

A total of 151,500 participants were included in our analysis, including 110,485 women and 41,015 men. Baseline characteristics are presented in Table 1. 281 LM and 776 MIS, non-LM cases were reported. Specifically, 182 and 99 cases of LM were reported in women and men, respectively.

LM occurred more commonly on the head/neck compared to MIS, non-LM (*p*<0.0001). Although the head and neck areas were the most common location for both genders (men, 57.0%, *n*=53 out of 93 LM with information on body sites; women 49.5%, *n*=90 out of 181 LM with information on body sites), the next most common area for men was the trunk (28.0%, *n*=26) compared to the upper extremity in women (20.3%, *n*=37). In men, the upper extremities comprised of 14.0% (*n*=13) of LM diagnoses.

Table 2 shows the hazard ratios of LM associated with quintiles of UV flux. Compared with participants that had the lowest UV flux (the first quintile), the risk of LM increased with the increasing UV flux exposure in men (multivariate-adjusted *p* for trend=0.04), but not in women (*p* for trend=0.91). Pooling the two cohorts, the multivariate-adjusted HR of LM was 1.33 (95% CI 0.92–1.93) associated with the highest quintile of UV flux compared to the lowest quintile.

Discussion

This study examined a US-based prospective cohort with histopathologically confirmed LM. The number of moles on the extremities, Fitzpatrick skin type, family history of melanoma, cancer history, and number of sunburns was similar across quintiles of UV flux, suggesting that these factors did not influence each subject's sun exposure behaviors. LM was more likely to develop on the head/neck in both genders, which is consistent with the literature.^{3,10} Women developed LM on the extremities more commonly than men. This study reinforced the clinical observation that LM is usually diagnosed on sun-exposed areas. In addition, it elucidated gender differences, perhaps both biological and behavioral, affecting location of LM. Similarly, other studies have shown gender differences in the location of tumor development of MM and keratinocyte carcinomas.^{11,12}

Lin et al explored the role of UV light on lentigo maligna melanoma, finding that lifetime UV index was a significant predictor.⁹ In that study, the UV index variable was measured at birth, age 15, and age 30, leaving 15-year gaps between each data point. Comparatively, our

study uses the UV flux variable, which accounts for UV exposure every 2 years, providing a more comprehensive appraisal of a person's lifetime UV exposure.

The present study found an association of UV flux with LM in men, but not in women. Sex hormones have long been attributed to changes in skin pigmentation as evidenced by the pigment changes frequently seen with the altered hormonal milieu of pregnancy. Natale *et al* described how estrogen impacts melanoma growth by comparing pregnant vs. non-pregnant mice with grafted human skin containing melanocytes with the BRAF oncogene. Pregnant mice were less likely to develop melanoma, which was attributed to their having increased hormonally induced melanin production and its associated UV-absorbing protective effect.^{13,14}

The lack of an association between UV flux and women suggest that sex-specific factors may also play a role in the development of these tumors. Similarly, Liu-Smith et al also found a strong association between UV light exposure in men, but not women.³ Evidence in the literature supports the hypothesis that female skin is more resilient to UV damage, with women's skin requiring 3 times higher UV doses to demonstrate comparable immunosuppressive responses as men's skin.¹⁵ Further, 17- β -estradiol, found in females, can inhibit UV-induced damage in mice.¹⁶ In vitro, 17- β -estradiol can also inhibit growth of human metastatic melanoma cells through inhibition of interleukin-8.¹⁷ These factors may partly help explain the null associations that were observed for UV flux and LM in females.

The women and men in this study were similar in regards to occupational experience, race, ethnicity, education, medical knowledge, access to health care, and socioeconomic status. These factors greatly help to minimize confounders in the data, since diagnosis of cancer can vary greatly among different geographic locations, race, ethnicity, socioeconomic status, and health insurance status.¹⁸ Due to the high healthcare literacy of this group, it is likely that they were more attuned to changes in their skin and thus sought evaluation at an earlier point than the general population, thus accounting for their younger age of diagnosis as compared to prior epidemiological studies. The younger average age of diagnosis in our population is consistent with prior research demonstrating that the age group between 45–65 years old showed the fastest growing incidence of LM.²

Despite this study's strengths, it is not without limitations. Although this study represented the largest U.S. based cohort of LM reported in the literature, the sample size is still relatively small when stratified based on gender and other variables examined. Further, it is possible that some LMs may have been miscategorized as MIS, non-LM types during the 1980's and early 1990's prior to the wide availability and rigorous use of special melanocytic stains by dermatopathologists.

This study represents the largest analysis of LM in a US-based cohort with over 3 decades of follow-up and data collection. Higher UV flux was associated with development of LM in men, but not women, which may suggest intrinsic differences in tumor biology based on gender.

Acknowledgements:

This study was supported by the Career Development Award of Dermatology Foundation (H. William Higgins II and Wen-Qing Li), and National Institutes of Health grants for the Nurses' Health Study (UM1 CA186107 and P01 CA87969) and the Health Professionals Follow-up Study (UM1 CA167552).

We would like to thank the participants and staff of the Nurses' Health Study and Health Professionals Follow-up Study, for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, and WY. The authors assume full responsibility for analyses and interpretation of these data.

IRB approval: This study was approved by the Institutional Review Boards of Brigham and Women's Hospital and the Harvard School of Public Health.

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Table 1:

Baseline characteristics of the study participants based on quintiles of UV flux in women (Nurses' Health Study; 1980–2012) and men (Health Professionals Follow-up Study; 1986–2010) *

Women	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
n	27,128	15,672	42,155	3,591	21,939
Age, mean (SD), year	46.3(7.2)	45.7(7.2)	45.9(7.3)	46.2(7.0)	47.9(7.1)
Natural red or blonde hair (%)	16.1	15.0	15.2	14.8	18.1
Family history of melanoma (%)	2.9	2.6	2.8	2.4	2.8
History of 6 severe or blistering sunburns (%)	3.8	3.6	3.4	3.7	4.8
6 moles on an extremity, 3+ mm diameter (%)	55.8	56.9	53.8	54.8	62.6
State of residence at birth with UV index 7 (%)	4.9	4.5	4.7	4.5	4.7
State of residence at age 15 with UV index 7 (%)	1.9	1.8	2.0	8.3	51.9
State of residence at age 30 with UV index 7 (%)	1.7	2.3	2.1	5.3	87.2
Men	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
n	8,637	9,358	6,890	8,351	7,779
Age, mean (SD), year	54.1(9.7)	53.8(9.7)	53.4(9.6)	52.8(9.5)	54.0(10.1)
Natural red or blonde hair (%)	13.1	11.7	13.6	15.4	14.3
Family history of melanoma (%)	3.3	2.5	3.1	3.1	3.0
History of 6 severe or blistering sunburns (%)	0.0	0.0	0.0	0.0	0.0
6 moles on an extremity, 3+ mm diameter (%)	30.4	30.1	35.2	39.8	38.6
State of residence at birth with UV index 7 (%)	4.8	4.8	5.0	5.3	5.6
State of residence at age 15 with UV index 7 (%)	4.6	4.0	21.2	61.2	51.2
State of residence at age 30 with UV index 7 (%)	8.0	9.3	25.0	64.8	57.9

Values are means (SD) or percentages and are standardized to the age distribution of the study population.

* Values are not age adjusted

Table 2:

Hazard ratios (HRs; 95% CI) of lentigo maligna associated with quintiles of UV flux

UV flux	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P for trend
Women						
Person-years	663,834	402,868	1,047,856	292,803	575,080	
Number of cases	32	33	55	24	38	
Age-adjusted HR	1.00	1.72(1.06,2.80)	1.11(0.72,1.71)	1.36(0.80,2.31)	1.21(0.76,1.94)	0.75
Multivariate-adjusted HR	1.00	1.72(1.05,2.79)	1.13(0.73,1.74)	1.34(0.79,2.28)	1.18(0.74,1.89)	0.91
Men						
Person-years	170,952	185,243	164,411	158,689	162,284	
Number of cases	17	19	11	22	30	
Age-adjusted	1.00	1.04(0.54,2.00)	0.67(0.31,1.42)	1.46(0.77,2.75)	1.80(0.99,3.26)	0.01
Multivariate-adjusted	1.00	1.01(0.52,1.94)	0.64(0.30,1.37)	1.34(0.71,2.53)	1.62(0.89,2.95)	0.04
Pooled						
Person-years	834,786	588,111	1,212,267	451,492	737,364	
Number of cases	49	52	66	46	68	
Age-adjusted	1.00	1.41 (0.87, 2.28)	0.95 (0.60, 1.50)	1.40 (0.93, 2.10)	1.41 (0.97, 2.06)	0.24
Multivariate-adjusted	1.00	1.38 (0.82, 2.30)	0.93 (0.55, 1.57)	1.34 (0.89, 2.01)	1.33 (0.92, 1.93)	0.32

* Multivariate model was jointly stratified by age in months and calendar year of the questionnaire cycle and was adjusted for childhood reaction to sun (no reaction, burn, painful burn/blisters), number of severe sunburns (none, 1–2 burns, 3–5 burns, 6–9 burns, 10+ burns), number of moles (none, 1–2 moles, 3–5 moles, 6+ moles), hair color (red, blonde, light brown, dark brown, black), and family history of melanoma.