Ultraviolet Radiation Exposure and the Incidence of Oral, Pharyngeal and Cervical Cancer and Melanoma: An Analysis of the SEER Data

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Abstract. *Background: Based on the hypothesis that ultraviolet radiation (UVR) exposure can cause DNA damage that may activate dormant viruses such as human papilloma virus, a recent ecological study, which estimated state-level UVR exposure, reported positive correlations between annual UVR exposure and the incidence of oral, pharyngeal, and cervical cancer in 16 U.S. states using the International Agency for Research on Cancer (IARC) data. The purpose of the current study was to further investigate whether the annual UVR level, estimated on a county level, is associated with incidence rates of such cancers using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) 18 data. If UVR exposure is associated with incidence of these cancer types, we would expect to see a similar or stronger association with melanoma because UVR exposure is a well-demonstrated risk factor for this disease. Thus, we also included melanoma in the study. Materials and Methods: The study subjects were White and Black individuals with oral, pharyngeal, cervical cancer or melanoma diagnosed between 1973 and 2011 from the SEER 18 data. UVR was estimated at the county level and grouped into high-, medium- and low-exposure levels. Age-adjusted incidence rates of cancer were calculated and compared among the UVR exposure groups. The comparisons were also stratified by sex and race. Results: There was an inverse association between UVR exposure and incidence of oral, pharyngeal, and cervical cancer. The inverse association was also observed for melanoma. When stratified by race and sex, the inverse associations remained except for melanoma among Blacks. Conclusion: In contrast to a previous study, our study found that there were inverse associations between UVR exposure and the incidence of oral, pharyngeal, and cervical cancer, as well as of melanoma. Our findings are in agreement with several other published studies reporting no positive correlation between UVR exposure and the incidence rates of oral, pharyngeal, and cervical cancer and melanoma.*

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Ultraviolet radiation (UVR) is a known risk factor for skin cancer (1). There exist multiple biological mechanisms for UVR carcinogenesis, including DNA damage, mutagenesis, immunosuppression, and interaction with viruses such as human papilloma virus (HPV) (2-4). Particularly in terms of interaction with HPV, it was found that HPV E6 and E7 proteins may impede the repair of UVR-induced DNA damage in HPV-infected cells (5-7). Consistent with the possible interaction mechanisms with HPV, a recent study found that UVR exposure was associated with increased incidence of oral, pharyngeal, and cervical cancer in 16 US states (8). This study used the data obtained from the International Agency for Research on Cancer (IARC) and calculated incidence rates during 1998-2002. UVR exposure was calculated using the latitude of the state in which the case was diagnosed (8). The authors concluded that there was a significant positive correlation between UVR exposure and incidence of oral, pharyngeal, and cervical cancer.

There exist several concerns about that study. Firstly, the study used state-level latitude to estimate UVR exposure and calculate state-level incidence rates. A state usually covers a large territory and latitude may vary substantially within the state. Thus, UVR exposure based on state-level latitude may not reflect the true UVR exposure in an area. Secondly, the data were based on the states available in the IARC data, which did not include certain states with high UVR exposure and low HPV-related cancer incidence. Thus, the results

might have been biased. In order to reduce the potential effects of these factors, we examined the associations between UV exposure and incidence of oral, pharyngeal, and cervical cancer reported by Godar *et al*. using county-level latitude to estimate UVR exposure and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) 18 data to calculate incidence rates by county-based UV exposure level. The SEER 18 data come from 18 cancer registries covering 28% of the US population. In addition, since UVR exposure is a well-known risk factor for melanoma, we added melanoma to our analysis to provide additional evidence on research results; the UVR–cancer association should be stronger than for other cancer types and be readily identified for the disease.

Materials and Methods

Data source. The data used for this study came from the National Cancer Institute's (NCI) SEER program. The 18 registries included in this dataset are Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, Alaska Native Tumor Registry, Greater California, Kentucky, Louisiana, New Jersey, and Greater Georgia. Due to small numbers of Black or White patients, the Alaska and Hawaii registries were excluded. Tumor and demographic characteristics, such as county of diagnosis, age, race, and gender, were ascertained from the SEER 18 database. Population data used for the rate calculations were obtained from the US Census Bureau (9).

Study subjects. The study subjects were patients diagnosed with oral cancer (C00-C08), pharyngeal cancer (C09-C14), cervical cancer (C53), and melanoma (C44 and site as melanoma of the skin) between 1973 and 2011. Patients were excluded if the tumor was not histologically confirmed or the patient had an unknown age. The analysis included only White and Black patients because other races were excluded due to relatively small numbers of patients, especially based on the county-level data.

Estimation of UV exposure. UV exposure was estimated using the county latitudes for the 187 counties included in the 18 SEER registries, which were obtained from the US Census Bureau (9), We used the equation described in the previous study by Godar *et al*. (8) to estimate the UVR level: UV dose=−280.25X+22066, where X is the latitude. Based on the range of UVR exposures, we divided the counties into tertiles labeled as low (<10647.77 J/m^2), medium (10647.77-12363.17 J/m^2), and high (>12363.17 J/m^2) exposure.

Statistical analysis. Crude and age-adjusted incidence rates of oral, pharyngeal and cervical cancer, and melanoma were calculated for each UVR exposure level and compared between different UVR levels. The comparisons were also conducted with stratification by sex and race. For age adjustment, the White and Black populations contained in the 2000 US Census Population data were used as the standard population. Chi-square tests were conducted and a two-sided *p*-value of less than 0.05 was considered significant. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

Over the 39-year study period, 52,880 individuals were diagnosed with pharyngeal cancer, 71,209 with cervical cancer, 115,524 with oral cancer, and 269,561 with melanoma, Table I shows the incidence rates by UVR exposure level in tertiles. The age-adjusted oral cancer incidence per 100,000 individuals was 3.33, 3.94, and 7.14 for the high (>12363.17 J/m^2), medium (10647.77-12363.17 J/m^2), and low (<10647.77 J/m^2) UV exposure groups, respectively inverse ($p<0.001$). This inverse relation was also observed for pharyngeal ($p<0.001$) and cervical ($p<0.001$) cancer, and melanoma ($p<0.001$).

When stratified by race (Table I), similar inverse associations were observed in both Whites and Blacks (both $p<0.001$ for all cancer types). The results were similar for melanoma ($p<0.001$ for both Whites and Blacks).

When analyses were stratified by both race and gender, the similar inverse association between UVR exposure group and incidence remained despite race and gender for pharyngeal cancer ($p<0.05$ for all the strata) (Figure 1, Panel a). For oral cancer, the inverse association was significant for Black females, Black males, and White males but not White females (Figure 1, Panel b). For melanoma, the low UVR exposure group had the highest incidence among both White females and males, while no statistically significant association was observed among Black females or males (Figure 1, Panel c).

Discussion

In contrast to the study by Godar *et al*., that showed a significant positive correlation between estimated UVR exposure and oral, pharyngeal and cervical cancer incidence (8), our study found a significant inverse association between UVR exposure and the incidence of these cancer types, as well as melanoma, using SEER 18 incidence data and county-level based UVR estimation. Both studies used the same UVR equation, while Godar *et al*.'s was based on state-level latitude and ours was based on county-level latitude to estimate UVR exposure and calculate the incidence rates corresponding to UVR exposure. Our results were somewhat consistent with the data presented by the Centers for Disease Control and Prevention (CDC) for HPV-associated cancer (10). According to the CDC data, HPV-associated cancer has a high incidence in the southeastern US where UVR exposure is high based on latitude, although it is much lower in the southwestern states where UVR exposure is also high (10). In the Godar *et al*. study, only southeastern states with high UVR were included to represent high UVR exposure states (8), southwestern states with high UVR were not included. Furthermore, as southeastern states also have higher HPV-related cancer incidence than southwestern states (10), the exclusion of southwestern states may have

Table I. *Incidence rates of oral, pharyngeal, cervical cancers and melanoma by UV Exposure, 1973 - 2011, the SEER 18 data.*

Estimated UV exposure (J/m^2)	Oral					Pharyngeal					Cervical					Melanoma				
		Crude		Age-adjusted			Crude		Age-adjusted			Crude		Age-adjusted			Crude		Age-adjusted	
	No.	r	*p*-Value	r	*p*-Value	No.	r	*p*-Value	r	*p*-Value	No.	r	*p*-Value	r	*p*-Value	No.	r	*p*-Value	r	*p*-Value
White and Black population																				
High (>12363.17)	34,071	2.96	<0.001	3.33	<0.001	17,132	1.48	<0.001	1.65	<0.001	24,615	4.28	<0.001	4.47	<0.001	88,840	7.60	<0.001	8.29	<0.001
Medium (10647.77-12363.17)	35,572	3.86		3.94		15,765	1.69		1.70		19,799	4.28		4.36		90,244	9.49	9.49		
Low (<10647.77)	45,881	7.12		7.14		19,983	3.10		3.08		26,795	8.17		8.27		90,477	13.80	13.63		
Black population																				
High (>12363.17)	4,274	2.12	<0.001	3.17	<0.001	3,390	1.68	<0.001	2.55	<0.001	5,035	4.75	<0.001	5.95	<0.001	678	0.35	<0.001	0.90	<0.001
Medium (10647.77-12363.17)	1,918	2.55		4.03		1,439	1.90		3.22		1,983	5.30		6.96		297	0.39	1.53		
Low (<10647.77)	3,751	4.95		6.95		2,791	3.65		5.33		4,360	11.20		14.23		425	0.54	1.56		
White population																				
High (>12363.17)	29,797	3.18	<0.001	3.43	<0.001	13,742	1.46	<0.001	1.58	<0.001	19,580	4.20	<0.001	4.33	<0.001	88,162	9.28	<0.001	9.73	<0.001
Medium (10647.77-12363.17)	33,654	4.02		3.97		14,326	1.67		1.65		17,816	4.20		4.24		89,947	10.34	10.15		
Low (<10647.77)	42,130	7.26		7.15			17,192		2.96	2.89	22,435	7.78		7.75	90,052	15.65	15.03			

*Rates per 100,000. The 2000 US Census Population was used as the standard population for the age adjustment.

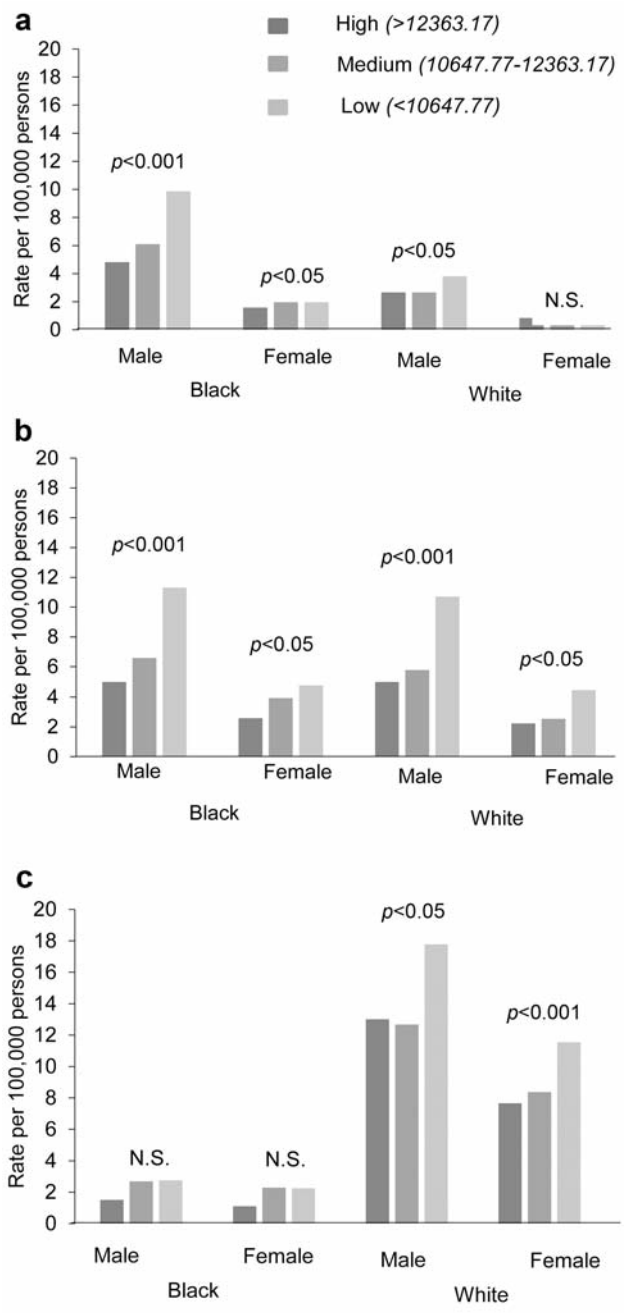

Figure 1. *Incidence rates by UV exposure stratified by race and gender for pharyngeal (a) and oral (b) cancer, and melanoma (c) from SEER 18 database 1973-2011. Estimated UV exposure: low: <10647.77 J/m^2, medium: 10647.77-12363.17 J/m^2), and high: >12363.17 J/m^2. N.S.: Not significant.*

driven the overall positive association observed in their study. In our study, both southwestern and southeastern areas were included and a positive association was not observed.

In our study, the UVR level was calculated based on county-level latitude rather than state-level latitude. UVR estimation based on state-level latitude may be subject to intrastate variations in altitude, latitudes and other factors. For example, states such as California have a wide range of latitudes represented and thus a single state-level latitude may not well represent the actual UVR level of an area. The estimation based on county-level latitude might reduce such misclassification for the area. Furthermore, the incidence rates were calculated for the areas with similar UVR levels rather than states or cancer registry areas.

In contrast to Godar *et al.*'s results (8), our results are in agreement with some previous ecological studies (11, 12). A study by Grant *et al.* compared cancer incidence in northern and southern regions of five Nordic countries and found a significant inverse correlation between UV index and the incidence of 15 types of cancer, which included cervical and pharyngeal cancer (11). Another study conducted in the US reported an inverse association between UVR exposure calculated at the state level and oral and cervical cancer mortality rates (12).

While a positive association with UVR might be expected to be identified for melanoma incidence, our results showed an inverse rather than positive association with UVR, especially among Whites. This is consistent with those in the CDC map of melanoma incidence in the US, which shows a higher incidence rate of melanoma in the north (where the UVR level is low) than the south (where UVR level is high) (13). In fact, studies have suggested that intermittent high-dose exposure to UVR may be a more important risk factor for melanoma than ambient UVR determined by geographic location (14, 15). The lack of the association among Blacks when stratified by gender is reasonable because of the higher melanin content in skin compared to the White population which provides a protective effect against melanoma (16, 17). Thus, both our results and CDC map pattern suggest a lack of positive correlation between latitude-based UVR estimation and melanoma incidence.

The inverse association observed in our study and in previous ecological studies (11, 12) might be attributed to the effect of vitamin D on the oncogenic processes (12, 18). Vitamin D plays a role in cellular apoptosis and may confer a protective effect against cancer (19). Sunlight exposure is a necessary component for vitamin D synthesis (20). It is also noteworthy that our study was an ecological investigation which did not reflect individual-level associations, and as noted in other epidemiological studies, many individual-level risk factors may have influenced the results (11, 12).

This study has several strengths relative to the previous study (8). Firstly, compared to the previous study (8), we refined the estimation of UVR exposure by using the county-level latitudes of the county. Secondly, in order to address the limited state selection in the previous study (8), we expanded the states by including south central and southwestern states with high UVR exposure and low cancer

incidence. Finally, the addition of melanoma, for which UVR is an established risk factor, provided additional evidence to confirm whether the identified associations in oral, pharyngeal and cervical cancer were true.

In conclusion, by using the SEER 18 data and refining UVR exposure, our results do not support a positive correlation between UVR exposure and the incidence of oral, pharyngeal and cervical cancer or melanoma.

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Disclaimer

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References

1 Moan J, Grigalavicius M, Baturaite Z, Dahlback A and Juzeniene A: The relationship between UV exposure and incidence of skin cancer. Photodermatol Photoimmunol Photomed *31*: 26-35, 2015.

2 Schwarz A and Schwarz T: Molecular determinants of UV-induced Immunosuppression. Exp Dermatol *11*: S9-12, 2002.

3 Elmets CA, Bergstresser PR, Tigelaar RE, Wood PJ and Streilein JW: Analysis of the mechanism of unresponsiveness produced by haptens painted on the skin exposed to low-dose ultraviolet radiation. J Exp Medi *158*: 781-794, 1983.

4 Ruhland A and Ethek-Michele DV: Opposite regulation of the HPV 20-URR and HPV 27-URR promoters by ultraviolet irradiation and cytokines. Int J Cancer *91*: 828-834, 2001.

5 Akgul B, Bostanci N, Westphal K, Nindl I, Navsaria H, Storey A and Pfister H: Human papillomavirus 5 and 8 E6 down-regulate interleukin-8 secretion in primary human keratinocytes. J Gen Virol *91*: 888-892, 2009.

6 Lee WT, Lee SH, Carriedo SG, Giffard RG, Yoon YJ, Kim JH, Park KA and Lee JE: UV-Vulnerability of human papilloma virus type-16 E7-expressing astrocytes is associated with mitochondrial membrane depolarization and caspase-3 activation. Mol Cells *14*: 288-294, 2002.

7 Mouret S, Favier A, Beani J-C, and Leccia M-T: Differential p53-mediated responses to solar-simulated radiation in human papillomavirus type 16-infected keratinocytes. Exp Dermatol *16*: 476-484, 2007.

8 Godar DE, Tang R and Merrill SJ: Pharyngeal and cervical cancer incidences significantly correlate with personal UV doses among Whites in the United States. Anticancer Res *34*: 4993-5000, 2014.

9 Bureau USC. Centers of Population. 2015 [updated 2-09-2015]; Available from: http://www.census.gov/geo/reference/ centersofpop.html.

10 CDC. HPV-Associated Oropharyngeal Cancer Rates by State. 2014 [updated 3/27/2014]; Available from: http://www.cdc.gov/cancer/hpv/statistics/state/oropharyngeal.htm.

11 Grant WB: Role of solar UVB irradiance and smoking in cancer as inferred from cancer incidence rates by occupation in Nordic countries. Dermatoendocrinol *4*: 203-211, 2012.

12 Grant WB and Garkand CF: The association of solar ultraviolet B (UVB) with reducing risk of cancer: multifactorial ecologic analysis of geographic variation in age-adjusted cancer mortality rates. Anticancer Res *26*: 2867-2700, 2006.

13 CDC. Skin Cancer Rates by State. 2014 [updated 8/26/2014]; Available from: http://www.cdc.gov/cancer/skin/statistics/state.htm.

14 Elwood JM and Jopson J: Melanoma and sun exposure: an overview of published studies. Int J Cancer *73*: 198-203, 1997.

15 Califano J and Nance M: Malignant melanoma. Facial Plast Surg Clin North Am *17*: 337-348, 2009.

16 Taylor SC: Skin of color: Biology, structure, function, and implications for dermatologic disease. J Am Acad Dermatol *46*: S41-S62, 2002.

17 Rijken F, Bruijnzeel PLB, van Weelden H, and Kiekens RCM: Responses of black and white skin to solar-simulating radiation: Differences in DNA Photodamage, infiltrating neutrophils, proteolytic enzymes induced, keratinocyte activation, and IL-10 expression. J Invest Dermatol *122*: 1448-1455, 2004.

18 Güneri P and Epstein JB: Late-stage diagnosis of oral cancer: Components and possible solutions. Oral Oncol *50*: 1131-1136, 2014.

19 Nemazannikova N, Antonas K and Dass CR: Role of vitamin D metabolism in cutaneous tumour formation and progression. J Pharm Pharmacol *65*: 2-10, 2013.

20 Bogh MK: Vitamin D production after UVB: aspects of UV-related and personal factors. Scand J Clin Lab Invest Suppl *243*: 24-31, 2012.

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