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Pharyngeal and Cervical Cancer Incidences Significantly Correlate with Personal UV Doses Among Whites in the United States

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Abstract. *Because we found UV-exposed oral tissue cells have reduced DNA repair and apoptotic cell death compared with skin tissue cells, we asked if a correlation existed between personal UV dose and the incidences of oral and pharyngeal cancer in the United States. We analyzed the International Agency for Research on Cancer's incidence data for oral and pharyngeal cancers by race (white and black) and sex using each state's average annual personal UV dose. We refer to our data as 'white' rather than 'Caucasian,' which is a specific subgroup of whites, and 'black' rather than African-American because blacks from other countries around the world reside in the U.S. Most oropharyngeal carcinomas harboured human papilloma virus (HPV), so we included cervical cancer as a control for direct UV activation. We found significant correlations between increasing UV dose and pharyngeal cancer in white males (p=0.000808) and females (p=0.0031) but not in blacks. Shockingly, we also found cervical cancer in whites to significantly correlate with increasing UV dose (p=0.0154). Thus, because pharyngeal and cervical cancer correlate significantly with increasing personal UV dose in only the white population, both direct (DNA damage) and indirect (soluble factors) effects may increase the risk of HPV-associated cancer.*

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Key Words: Cervical cancer, cytokines, environment, human papilloma virus, oral cancer, oropharyngeal cancer, pharyngeal cancer, sunlight, ultraviolet.

Oral cavity cancer comprises those found in the lips, cheeks (buccal mucosa), gums, front two-thirds of the tongue, floor of the mouth below the tongue, and the hard palate. Pharyngeal cancer comprises those found in the tonsils, pyriform sinus, nasopharynx, hypopharynx, and the oropharynx. Oropharyngeal cancer comprises those found in the base, or back third, of the tongue, the soft palate, the side and back wall of the throat, and the part of the throat right behind the mouth. The American Cancer Society estimates about 37,000 people in the United States will be diagnosed with oral cavity or oropharyngeal cancer and about 7,300 will die in 2014 (1), making it almost twice as deadly as cutaneous malignant melanoma (2). The incidence rates of oral and pharyngeal cancer are about twice as high in men as in women, and oral cancer ranks as the eighth most common cancer among men in the U.S. (3).

The primary causes of most oral and pharyngeal cancer are tobacco (smoking or chewing), alcohol (4-7), human papilloma virus (HPV; 8), and UV (290-400 nm) radiation (9-11). Tobacco use increases a person's risk for developing cancer *via* formation of DNA adducts that lead to mutations (6), while alcohol enhances the risks associated with other carcinogens (7). According to the International Agency of Research on Cancer (IARC), HPV (12) and UV (13) are both independent, complete human carcinogens. HPV can cause cancer by preventing cell death (14, 15) and causing cells to evade immune surveillance (16, 17) and infects the pharyngeal components, *i.e.* the tonsils, the tonsillar crypts, the tonsillar pillars, the base of the tongue, and the back of the throat (oropharynx). The prevalence of HPV in oropharyngeal cancer increased from about 16% during 1984-1989 to about 72% during 2000-2004 in the U.S. (18), as evidenced by biopsies (19). UV radiation can cause cancer by creating four types of potentially mutagenic DNA damages: cyclobutane pyrimidine dimers, 6-4 photoproducts, Dewar photoproducts, and 8-hydroxy-2'-deoxyguanine (13). UV-induced DNA damage can also activate many dormant viruses (20); UVB (290-320 nm) can activate the herpes simplex virus (21), the human immunodeficiency virus (22), and some strains

of HPV (23); UVA (321-400 nm) with a photosensitizer can also activate the human immunodeficiency virus (22) and HPV (24). An ecological study first demonstrated a possible correlation between increasing UV index and increasing incidence of salivary gland cancer (11). Almost a decade later (10), a significant increase in the risk of salivary gland cancer from UV radiation was established by an epidemiological population-based, case–control study of patients' head and neck regions medically irradiated with UV [Odds Ratio (OR)=1.9; 95% Confidence Intervals (CI)=0.89-4.3]. Environmental UV radiation contributes toward the increase in the incidence of lip cancer based on the observation that the lower lip has a higher incidence of cancer than the upper lip (25, 26) and of UV signature mutations in p53 (9).

In addition to outdoor solar UV exposures, people can receive indoor UV exposure from sunlight through windows, and medical, dental and cosmetic devices. For example, most window glass filters-out UVB radiation but allows significant amounts of UVA radiation to enter people's cars (27) and offices (28). Some medical procedures use UV-emitting devices to diagnose head and neck tumors (29) and oral cancer (30), while others treat chronic graft-*versus*-host disease (31, 32), allergic rhinitis (33), and oral lichen planus (34). Dental procedures include UV photography to monitor plaques during direct bonding (35), UVB excimer laser radiation (308 nm) to detect and ablate residual organic tissues in root canals (36), and ultraviolet LED illumination to remove composite resins (37). But some of the highest indoor UV doses to oral and oropharyngeal tissues can come from dental lamps and cosmetic tanning devices when people simply open their mouths. Additionally, a commercially available teeth whitening procedure uses a peroxide gel and UV-emitting tanning devices to theoretically augment the bleaching process by creating more reactive oxygen species than the gel alone; however, an independent study did not substantiate that claim (38).

Because we found oral and gingival tissue cells to have significantly lower DNA damage repair and apoptotic cell death rates for UVB-induced damage, compared to skin tissue cells (39-41), we asked if the incidences of oral and pharyngeal cancer in the general U.S. population correlate with UV doses. To assess if such cancer in the general U.S. population correlates with average annual UV doses after planar correction (42), we analyzed IARC's epidemiology data for white and black males and females by weighting the population of each U.S. states' incidence and plotting by that state's population-centered latitude average annual personal UV dose estimates (43-45).

Materials and Methods

Oral, pharyngeal, and cervical cancer incidence analysis. IARC's oral and pharyngeal cancer incidence data (combined) (C00-14) comprise those found in the lip (C00), tongue (C01-02), mouth (C03-06), salivary glands (C07-08) and pharynx (C09-14). Further delineation of the codes: tongue includes base of tongue (C01), other and unspecified parts (C02); mouth includes gum (C03), floor of mouth (C04), palate (C05), other and unspecified parts (C06); salivary glands include parotid gland (C07), other and unspecified (C08); pharynx includes tonsil (C09), oropharynx (C10), nasopharynx (C11), pyriform sinus (C12), hypopharynx (C13), and pharynx unspecified (C14).

We analyzed IARC's age-standardized incidence rates per 100,000 people, or ASR(W), of the oral and pharyngeal cancer (combined; C00-C14), lip (C00), tongue (C01-02), mouth (C03-06), salivary glands (C07-08), and just pharyngeal cancer (C09-14) in 2000 for white and black males and females in the District of Columbia (DC) and 15 states in the U.S. (46). We excluded Hawaii, Alaska, and New Mexico because there are either no data for whites (or non-Hispanic whites) or African Americans (blacks) to make comparisons. We only used the non-Hispanic white populations in our analysis so we refer to our data as 'white' rather than 'Caucasian,' which is a specific subgroup of whites, and 'black' rather than African-American because blacks from other countries around the world reside in the U.S., *e.g.* Jamaicans, so that these terms more precisely define the population groups that were analyzed.

Average annual personal UV dose. IARC had white and black incident data in the U.S. spanning from 24˚N to 46˚N, or spanning average geographic latitudes from 28˚N to 44˚N for only District of Columbia and 15 states.

We calculated average annual personal UV doses from the population centers of each state's latitudes (47). The U.S. states analyzed were Florida (27.8˚N), Louisiana (30.7˚N), Texas (30.94˚N), Alabama (33˚N), Georgia (33.33˚N), South Carolina (34.03˚N), California (35.46˚N), Missouri (38.44˚N), District of Columbia (38.91˚N), Illinois (41.28˚N), New Jersey (40.44˚N), Ohio (40.48˚N), Pennsylvania (40.46˚N), Connecticut (41.5 ˚N), New York State (41.51˚N), and Michigan (42.87˚N). The data available for other races was too sparse for latitudinal analysis. In the year 2000, most of those with oropharyngeal cancer were infected with HPV (about 72%; 23), so we included cervical cancer incidence as our internal control on HPV activation by direct UV exposure (48).

The average annual UV doses for populations living in the regions analyzed were calculated using the equation derived from the slope of the line (R^2=0.988) after geometric conversion from planar to cylinder measurements, which represent the human body (42). The countries with average annual personal UV doses that generated this equation were Sweden (60˚N; 5,223 J/m^2), Denmark (55˚N; 6,787 J/m^2), the Netherlands (52.5˚N; 6,991 J/m^2), and the U.S. (34˚N, 10,084 J/m^2 and 44˚N, 12,412 J/m^2):

UV dose=−280.25*X*+22066

where '*X*' is the latitude. Note that these average annual personal UV doses are all erythemally weighted UV doses in J/m^2 and do not include vacations that can be taken at any latitude (42-45). To obtain erythemally weighted UV doses, the solar spectrum in W/m^2 is multiplied, wavelength for wavelength from 290-400 nm, by the erythemal action spectrum, which indicates the ability to sunburn and is a common weighting factor for terrestrial and personal readings, and then the number of seconds a person is exposed to get J/m^2 (45).

Population weighting. Using Minitab® 16.2.4 (Penn State, State College, Pennsylvania, U.S.), we performed weighted regression of the cancer incidences on the average annual UV doses at different

latitudes in the U.S. We based weightings on white and black state populations from the 2000 U.S. census data (49).

Statistical analysis. To assess the statistical significance of the relationship between the cancer incidence rates and latitude, we provide the Bonferroni corrected two-sided *p*-values for each independent cancer type, gender, and ethnicity, indicating the significance of the estimated slopes, or the correlations. Bonferroni correction is necessary to control the overall probability of type I error, or the probability of false positive results, when making repeated significance testing (50). The Bonferroni correction factor depends on the number of calculations made for each cancer type. The Bonferroni correction value is 4 for oral and pharyngeal cancer combined (male and female, black and white), pharyngeal cancer, and for all other cancer types, whereas it is only 2 for cervical cancer (black and white females). We considered a Bonferroni corrected two-sided *p*-value less than 0.05 to be significant to ensure the overall type I error rate is less than 0.05 for each cancer type.

Results

Figure 1 shows the scatter plot of the incidences of oral and pharyngeal cancer combined by the average annual personal UV dose in each state. The incidence of oral and pharyngeal cancer combined (10-15/100,000) in white males was more than twice that in white females (<5/100,000). Statistical analysis of the white population's incidences (see Table I) showed a significant correlation between oral and pharyngeal cancer combined, and increasing UV dose for males (p=0.000424) but not for females (p=0.076). Note that for white females, oral and pharyngeal cancer combined were significantly associated with UV dose before Bonferroni correction (see Table I). Conversely, statistical analysis of the black population's incidences showed no significant correlation existed between the oral and pharyngeal cancer combined and increasing UV dose, neither before nor after Bonferroni correction (see Table II).

Figure 2 shows the scatter plot of the pharyngeal cancer incidences in white and black males for the weighted populations by the average annual personal UV dose of each state's population. Statistical analysis of the incidence of pharyngeal cancer showed pharyngeal cancer in both white males (p=0.000808) and females (p=0.0031; results not plotted) significantly correlated with increasing average annual UV doses (see Table I). Conversely, pharyngeal cancer in blacks did not correlate with average annual personal UV dose at all, as noted by the flat trendline across the entire U.S. and there was no significant correlation before or after Bonferroni correction (see Table II for *p*-values).

Figure 3 shows the cervical cancer incidences in blacks and whites plotted by the average annual personal UV dose of each state's population in the U.S. Although cervical cancer incidence in blacks was higher than in whites in 2000, they did not correlate with increasing UV dose (see Table II).

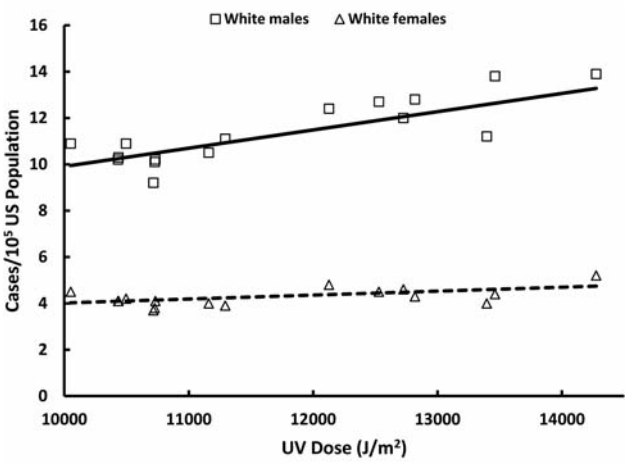

Figure 1. *Incidence of oral and pharyngeal cancer (combined) plotted by average annual personal UV dose for white populations in the U.S. The population-weighted incidences of oral and pharyngeal cancer combined significantly correlated with UV dose (see Table I) for white males (p=0.000424), but not for white females (p=0.0746; note the flat trendline with UV dose) or blacks (Table II).*

Surprisingly, we found that increasing incidences of cervical cancer in white females significantly correlated with increasing average annual personal UV dose before and especially after Bonferroni correction (p=0.0154; see Table I).

The statistics and the two-sided, uncorrected and Bonferroni corrected *p*-values for population-weighted incidences of the oral and pharyngeal cancer combined, pharyngeal, and cervical cancer in the U.S. for whites and blacks are shown in Table I and II, respectively. None of the *p*-values for blacks significantly correlated with the average annual personal UV dose.

Discussion

We found four lines of evidence suggesting UV exposure may contribute toward pharyngeal and cervical cancer. Firstly, we found a significant correlation existed between UV doses and the increasing incidence of oral and pharyngeal cancers combined in white males (p=0.000424; Figure1 and Table I) that strongly suggested a role for UV in these types of cancer which may be more than just an interaction with HPV that infects only a few parts of the oral cavity. Secondly, we found a significant correlation existed between pharyngeal cancer in white, but not black, males and UV doses (male p=0.000808; Table I and Figure 2). Thirdly, when we analyzed the same cancer types in the black U.S. population, we found no correlation existed with UV dose (*e.g.* Figure 2; Table II), possibly because the skin pigment, melanin, reduces UV penetration and decreases or eliminates any consequent

Table I. *Statistics for weighted cancer incidences in the U.S. white population analyzed by population weighting and average annual UV dose for each state, with Bonferroni corrected two-sided p-values for significance of the slope.*

Cancer Type	Gender	R^2	Correlation	*p*-Value	*p*-Value*
Oral and pharyngeal	Male	0.671	0.819	0.000106	0.000424
	Female	0.335	0.579	0.01865	0.0746
Pharyngeal	Male	0.639	0.799	0.000202	0.000808
	Female	0.566	0.752	0.000778	0.00311
Cervical	Female	0.409	0.640	0.00768	0.0154

*The Bonferroni correction factor for this analysis was 2 for cervical cancer and 4 for the other types. Corrected *p*-values <0.05 were considered significant.

Table II. *Statistics for weighted cancer incidences in the U.S. black population analyzed by population weighting and average annual UV dose for each state, with Bonferroni corrected two-sided p-values for significance of the slope.*

Cancer Type	Gender	R^2	Correlation	*p*-Value	*p*-Value*
Oral&Pharynx	Male	0.040	0.200	0.459	>1
Oral&Pharynx	Female	0.005	0.071	0.805	>1
Pharynx	Male	0.031	0.176	0.512	>1
Pharynx	Female	0.038	0.195	0.472	>1
Cervix	Female	0.012	0.110	0.690	>1

*The Bonferroni correction factor for this analysis is 2 for cervical cancer and 4 for the other types. Corrected *p*-values <0.05 determine significance.

biological effects (51). Fourthly, we surprisingly found cervical cancer, the other type of HPV-16/18-infected tissue, significantly correlated with UV dose for white (p=0.0154; Table I) but not for black females (Figure 3; Table II). Furthermore, we observed the incidence of oral and pharyngeal cancer combined in white males was over twice (10-15/100,000) that in white females (<5/100,000), possibly because males receive about 50% higher annual UV doses than females receive in the U.S. (40-42). Before Bonferroni correction but not after it, we also found a significant correlation between the increasing incidence of lip cancer and UV dose for white males (p=0.017) but not for white females (p=0.073) or black males (p=0.768) or females (p=0.619).

In addition to lip cancer (9, 25, 26), UV radiation contributes toward salivary gland cancer. Spitz *et al*. found indirect evidence that the increasing incidence of salivary gland cancer correlates with the decreasing geographically centered UV index of each state (11). Horn-Ross *et al*. found direct evidence that UV radiation causes salivary gland cancer from a population-based, case-controlled study examining medical treatments using UV irradiation of the head and neck region (10). However, we found no significant correlation existed between salivary gland cancer and UV doses in the U.S., neither before nor after Bonferroni correction (results not shown), possibly because HPV only infects the parotid and not the submandibular or sublingual glands.

The surprising correlation between cervical cancer in whites and UV dose may be explained by the production of soluble factors such as inflammatory cytokines produced by UV-exposed skin cells (indirect effects); whereas, the correlation of oral and pharyngeal cancer in whites with increasing average annual personal UV dose may be from both direct (DNA damage) and indirect (inflammatory cytokine) effects (52-54). UVB-exposed skin cells produce immunosuppressive inflammatory cytokines (41) and other soluble factors such as interleukin 10 (IL10; 53, 55), which causes immune suppression (56) and is associated with a negative clinical outcome in patients with head and neck squamous cell carcinoma (57). In fact, non-melanoma skin cancer develops from both direct UVB-induced DNA damage and from indirect immune suppression caused by the systemic release of cytokines including IL10 (53, 55). Curiously, HPV evades immune surveillance by causing the infected cervical cell to make IL10 (16, 58), resulting in high levels of regulatory T-cells (57). Moreover, clinicians found evidence that UV radiation is involved in cervical cancer from seasonal fluctuations of HPV in cervical smears (52).

Conversely, UVB-exposed skin also leads to the production of vitamin D_3, a beneficial soluble factor, which evidently reduces the incidence of some cancer types (59). The hormonal form of vitamin D_3, calcitriol, boosts immune surveillance by increasing killer T-cell populations that

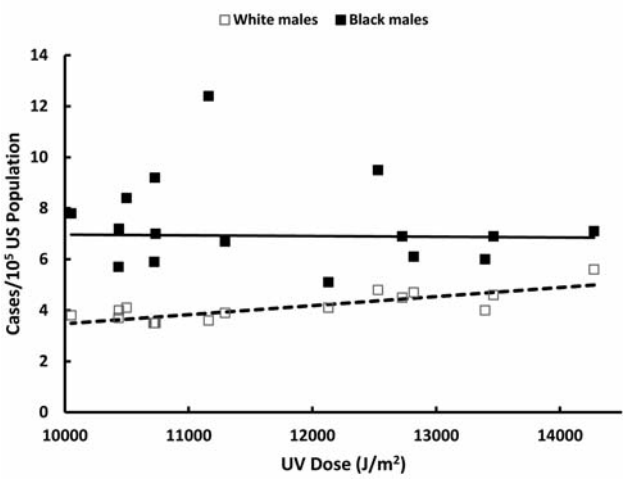

Figure 2. *Incidence of pharyngeal cancer plotted by average annual personal UV dose for white and black male populations in the U.S. The population-weighted incidence significantly correlated with UV dose (see Table I) for white males (p<0.000808) and white females (p=0.0154; results not plotted), while no significance exists for blacks (note the flat trendline with UV dose; Table II).*

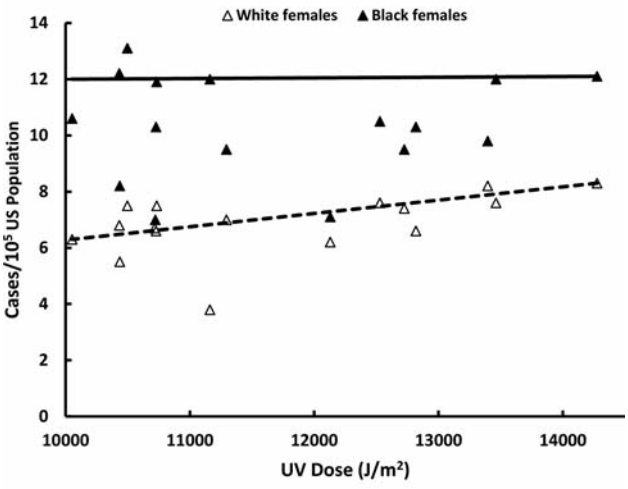

Figure 3. *Incidence of cervical cancer plotted by average annual personal UV dose for white and black female populations in the U.S. The population-weighted incidence significantly correlated with UV dose (see Table I) for white females (p=0.0154), but not for black females (note the flat trendline with UV dose; Table II).*

eliminate cancer cells (60). In addition, in some cell types, *e.g.* melanoma cells (61), calcitriol initiates an apoptotic death mechanism that removes DNA-damaged or HPV-infected cells or both, reducing the incidence of that type of cancer, as evidenced by polymorphisms in the intranuclear vitamin D_3 receptor [*VDR*; (62)]. Polymorphisms in the *VDR* of oral cells did not reduce the incidence of oral cancer (63), whereas, they did decrease the incidence of melanoma, breast, and prostate cancer (64). These findings also support our observed significant trend in pharyngeal and cervical cancer with increasing average annual personal UV doses evidently because oral cells do not trigger a calcitriol-associated apoptotic death pathway (63, 64).

In contrast, significant correlations exist between decreasing latitude or increasing UV dose and the kinds of cancer that have cell types with functional VDR-associated apoptotic death pathways such as of the breast and colon, and melanoma (64, 65), as evidenced by *VDR* polymorphisms (64). The fact that some types of cancer significantly correlate with increasing latitude, a proxy for decreasing annual UV dose and usually lower vitamin D levels, after considering confounding factors in those analyses (65) adds weight to our observations that the opposite situation can occur in the presence of the same confounding factors. We found that cancer significantly correlated with UV dose in whites and not blacks, which suggests UV may directly activate particular strains of HPV or indirectly produce cytokines such as IL10 enabling HPV to hide from immune surveillance.

Because we used IARC epidemiological data, we could not control for confounding factors so that our analyses only document an association between increasing incidences of pharyngeal and cervical cancer and increasing average annual personal UV dose. Nevertheless, these findings are alarming because along with the known direct mutagenic effects of UV radiation and activation of HPV, they suggest indirect production of soluble factors by UV-irradiated skin cells may promote other types of HPV-associated cancer if those cell types lack a functional VDR-associated apoptotic pathway.

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