Published in final edited form as:
J Am Acad Dermatol. 2011 July ; 65(1): 35–39. doi:10.1016/j.jaad.2010.05.026.

Asymmetric lateral distribution of melanoma and Merkel cell carcinoma in the United States

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Abstract

Background—A recent report suggested a trend towards more UV-linked skin cancers arising on the left rather than the right side of the body in the United States.

Objective—To test whether the reported incidences of two UV-linked skin cancers, malignant melanoma (MM) and Merkel cell carcinoma (MCC), are greater on the left than the right in the US.

Methods—MMs (n = 82,587) and MCCs (n = 2,384) occurring on the left or right side of the face, arm or leg that were reported in the SE*ER registry between 1986–2006 were included for analysis.

Results—MM and MCC were significantly more likely to present on the left than the right ($p < 0.01$ for both MM and MCC). 53% of arm melanomas, 51% of facial melanomas, and 52% of leg melanomas presented on the left. 55% of arm MCCs, and 52% of facial MCCs presented on the left, while leg MCCs were equally distributed.

Limitations—National registry data did not provide information regarding sun exposure or driving habits. No equivalent registry data were available for basal or squamous cell carcinoma.

Conclusions—Both melanoma and MCC are significantly more likely to arise on the left than the right, and this effect was most prominent on the arm. Driver's-side automobile UV exposure (approximately 20-fold stronger on the left than right arm) is a likely contributing factor. It may be prudent to remind skin cancer-prone individuals to take appropriate sun precautions when driving in an automobile.

Keywords

Merkel cell carcinoma; melanoma; ultraviolet; asymmetric; presentation; automobile

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Prior presentation: This study has not been presented previously.

Conflict of Interest Disclosure: None Declared.

Introduction

Ultraviolet light (UV) is a well-characterized risk factor for most skin cancers, including melanoma1 and Merkel cell carcinoma 2, 3. One source of environmental UV exposure is driving or riding in automobiles. Actinic keratoses have been reported to occur more frequently on the right side of the body in Australian drivers, where drivers sit on the right side of the car 4. Conversely, in a recent case series from the United States, where drivers sit on the left side of the car, a trend toward left sided bias in skin cancer was observed5. In this series of 890 cases, skin cancers (mostly basal cell carcinomas) were more frequently detected on the left side of the body (53% vs. 47%), although the trend did not reach statistical significance.

A recent study (Moehrle et al) carefully examined the pattern of UV exposure received by a driver sitting on the left side of an automobile6. Moehrle et al reported that 25–31% of ambient UV radiation is transmitted through an open car window (the remainder is blocked by the vehicle body). In contrast, a closed car window that only transmits UV-A rays, allows 3–4% of environmental UV radiation to be transmitted6. For the driver, this radiation more strongly affects the left side of the body. In particular, a left-sided driver sitting next to a closed car window receives approximately 5 times more UV to the left arm than the right arm, and 20 times more UV on the left side of the face than the right. In contrast to the arm and face, a driver sitting on the left receives slightly more UV on the right leg than the left (1.4 times more on the right).

As noted above, a non-significant trend towards left-sided skin cancer bias has recently been suggested in the United States population5. In order to build on this study, we employed national registry data from the Surveillance, Epidemiology, and End Results (SE*ER) database to test in a large number of cases whether there are significantly more left than right-sided UV-associated cancers reported in the United States. Specifically, we focused on two skin cancers: malignant melanoma (MM) and Merkel cell carcinoma (MCC), because these are captured in the SE*ER database. We hypothesized both MM and MCC would display a left sided bias. Furthermore, we hypothesized this bias might be due to driving and thus particularly affect the face and left arm, but not the leg.

Materials and methods

Patient inclusion

Information was obtained from the SE*ER registry database7. We considered all melanoma (ICD-O-3 code 8270-8774) and Merkel cell carcinoma (ICD-O-3 8247) cases that met the following criteria: diagnosed between 1986-2006, lateralized cancer (as opposed to midline) with known side, known age, known gender. Cancers that presented on one of three body sites were considered for analysis: skin of face and scalp (C44.3, C44.4), upper limb (C44.6), and lower limb (C44.7). A total of 82,587 melanoma and 2,384 MCC cases were included in the analysis.

Data extraction

Data was extracted using SE*ERstat software.

Statistical analysis

Melanoma and MCC were analyzed separately. Statistical analysis was performed with GraphPad Prism software. Chi squared test was used to test whether the observed left-right distribution differed significantly from 50% on the left and 50% on the right.

Results

Malignant melanoma

Among 82,587 melanomas analyzed, 52.3% presented on the left side and 47.7% on the right. This left-bias was statistically significant, $p < 0.001$.

Appreciably more tumors were observed on the left side of the face and the left arm as compared to the right (Figure 1). 51% of face and scalp melanomas (7,787 of 15,185, $p = 0.002$) and 53% of arm (19,791 of 37,588, $p < 0.001$) melanomas presented on the left side. However, melanomas were also significantly more likely to present on the left leg than the right. 52% of leg tumors (15,627 of 29,814, $p < 0.001$) presented on the left side.

Data were split out by age and sex to determine whether left-right biases were more pronounced in any particular group. Women older than 65 trended towards less left-side bias in the head and neck as compared to older men, however, this difference between men and women was not significant ($p = 0.56$) (Table 1).

Merkel cell carcinoma

2384 MCCs met inclusion criteria and were analyzed. Of these, 1256 (52.7%) presented on the left and 1128 (47.3%) on the right ($p = 0.046$) (Table 2). Face, scalp, and upper limb cases were more likely to present on the left than the right, but cases on the leg were evenly distributed. Left side presentation occurred in 465 of 845 cases on the upper limb (55%, $p = 0.004$), 503 of 968 cases on the face and scalp (52%, $p = 0.22$), and 288 of 571 cases on the lower limb (50%, $p = 0.83$) (Figure 2).

Discussion

It has previously been suggested by Butler et al. that skin cancers in the United States, particularly in men, are more likely to present on the left side of the body. Importantly, this contrasts with Australia, where a similarly-sized study finds that actinic keratoses in men are significantly more likely to present on the right side of the body4. Both sets of authors suggest automobile UV exposure as a possible explanation, and the observed reversal in the asymmetrically involved side is consistent because drivers in the US sit on the left side of the car whereas drivers in Australia sit on the right. However, Butler et al. only looked at a limited number of cases (890), and the observed left-sided trend in the USA was non-significant except in a few subgroups5. In order to test for presence of left-sided bias in the United States, we analyzed the laterality of skin cancers reported in the SE*ER national registry database. Merkel cell carcinoma and malignant melanoma were the focus, because these aggressive UV-linked cancers are captured by the SE*ER program. Indeed, both of these cancers showed a highly significant left-side bias in their primary location that was particularly pronounced on the arms.

The left-sided bias of melanoma can be partially but not perfectly explained by UV exposure while driving. The observed asymmetry for melanoma was most prominent on the left arm, which receives both the largest UV dosage and the most asymmetric UV exposure from driving (approximately 20-fold more UV on the left arm than the right)6. Significant left-sided asymmetry was also detected for leg melanomas. For the leg, UV exposure in the automobile is more evenly distributed, with only an approximate 1.5 fold difference between sides and the expected UV exposure being greater on the right. Findings on the leg may be due to alternate sources of asymmetrical UV, however, population-wide asymmetrical UV exposures that could account for this observed bias are elusive and no additional potential exposures were gleaned from a PubMed search of "asymmetrical ultraviolet". Regardless of cause, this left-sided association was statistically significant at all studied sites (arm, leg, and

scalp/face) and is equivalent to approximately one in twenty melanomas that arise in excess on the left in the US.

Merkel cell carcinoma is an increasingly common skin cancer that has been strongly linked to environmental UV2, 3, 8, 9. We observed significantly more MCC presenting on the left than the right. For Merkel cell carcinoma, observed asymmetrical pattern is strongly consistent with excess left sided UV exposure from automobile driving 6, 10. The upper limb, which receives the greatest differential of UV from driving a car, demonstrated the most left side bias, with 1.2 MCCs occurring on the left for each on the right arm. Furthermore, and consistent with the UV blocking effect of an automobile door, MCCs presenting on the leg did not show a left-sided bias. Therefore, automobile UV exposure may represent an appreciable risk factor for MCC. However, we cannot rule out other possible explanations.

Our study has several limitations. SE*ER does not provide information on whether the skin was sun-exposed or not. Furthermore, we do not have information on individual driving or automobile riding habits, and cannot test the association of left bias with time in the driver's seat. In order to determine the importance of automobile UV exposure in this asymmetrical distribution, further study is indicated in countries with opposite driving patterns and/or of sets of data annotated with driving habit information. Despite these limitations, these findings represent the largest study of asymmetry in skin cancer in the United States to date.

In summary, both Merkel cell carcinoma and malignant melanoma are significantly more likely to present on the left side than the right in the United States. Automobile UV exposure is well-characterized source of asymmetrical UV exposure and likely contributes to the observed excess of melanoma and MCC presenting on the left arm. These excess left-sided cancers represent 1 out of every 20 upper limb melanomas and a striking 1 out of every 10 upper limb Merkel cell carcinomas. Therefore, it may be prudent to recommend sunscreen application or other UV protective measures in skin cancer-prone individuals who spend significant time driving automobiles or trucks.

Acknowledgments

Funding sources: This work was funded by the MCC Patient Gift Fund at the University of Washington, ACS RSG-08-115-01-CCE and K24 CA139052-0 to PN, and NIH F30ES017385 to KP.

Abbreviations

MCC	Merkel cell carcinoma
MM	malignant melanoma
UV	ultraviolet

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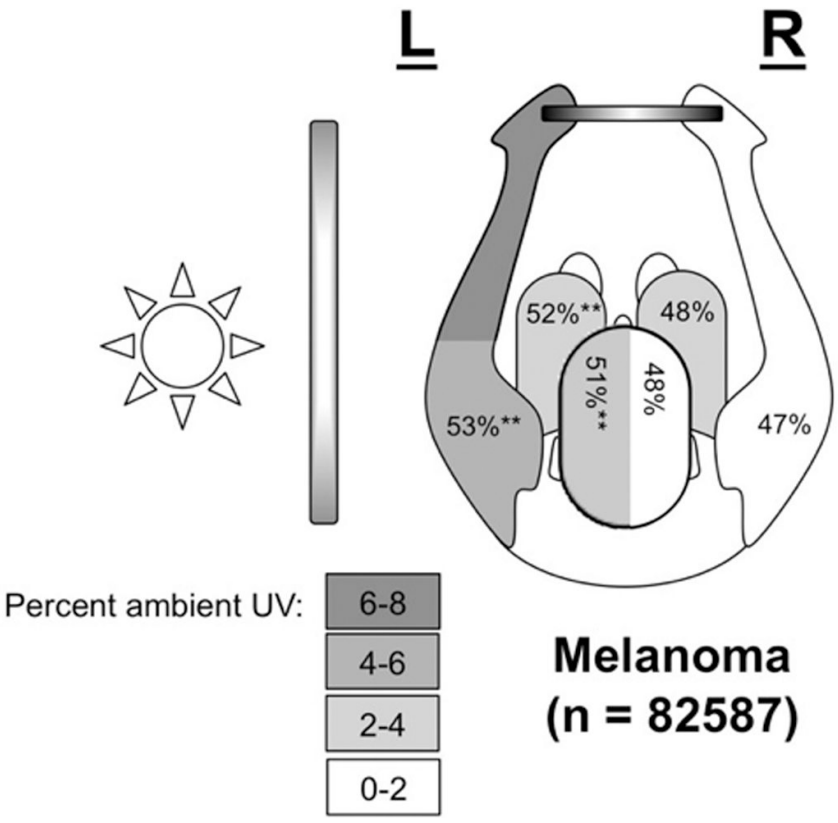

Figure 1. Fraction of non-midline melanomas that present on each side of the body

The percentage of lateralized melanomas presenting on the left and right sides are shown for face/scalp, arm, and leg. Asterisks mark statistical significance, * $p < 0.05$, ** $p < 0.01$. Shading reflects the approximate relative fold difference, comparing left and right sides, in terms of UV exposure received while driving in a left-sided car, as reported in Moehrle et al 6. Shaded areas receive relatively more UV, as indicated in the key.

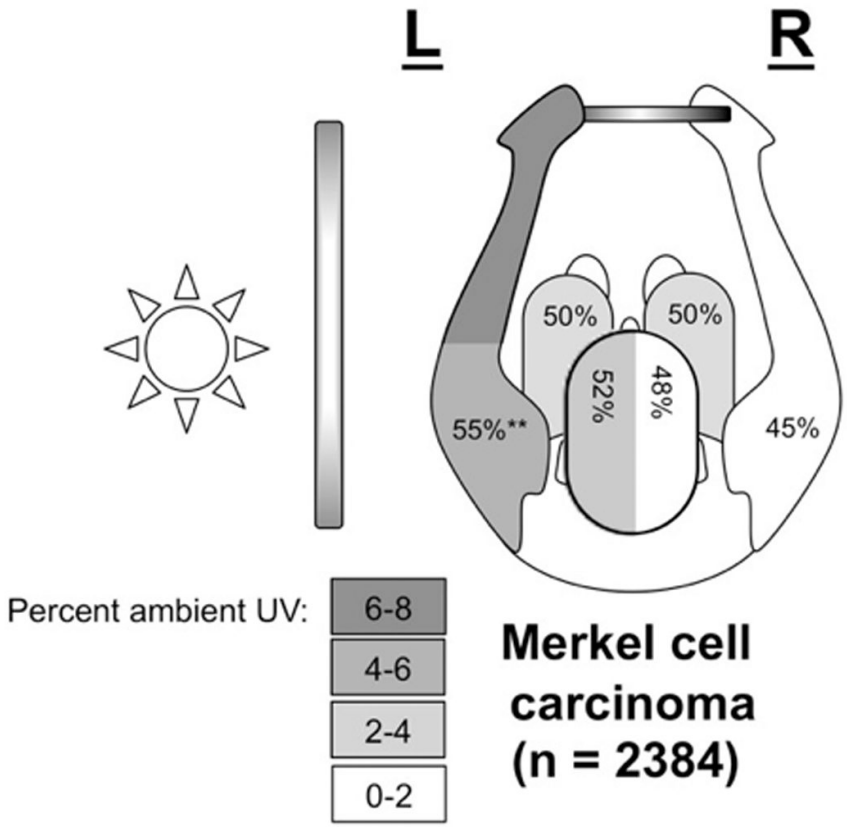

Figure 2. Fraction of non-midline Merkel cell carcinomas that present on each side of the body

The percentage of lateralized Merkel cell carcinomas presenting on the left and right sides are shown for face/scalp, arm, and leg. Asterisks mark statistical significance, * $p < 0.05$, ** $p < 0.01$. Shading reflects the approximate relative fold difference, comparing left and right sides, in terms of UV exposure received while driving in a left-sided car, as reported in Moehrle et al 6. Shaded areas receive relatively more UV, as indicated in the key.

Table I

Percent of melanomas that present on the left, broken down by age, sex, and body site.

	MM: % lateralized tumors presenting on left side			
	scalp and face	**upper limb**	**lower limb**	**Total**
over 65 - men	52%** (3080/5920)	53%** (4511/8514)	53%** (1339/2536)	53%** (8930/16970)
over 65 - women	51% (1786/3474)	51%* (3224/6262)	51%* (3065/5972)	51%** (8075/15708)
under 65 - men	50% (1826/3618)	53%** (5855/10960)	53%** (3012/5703)	53%** (10693/20281)
under 65 - women	50% (1095/2173)	52%** (6201/11852)	53%** (8211/15603)	52%** (15507/29628)
Total	51%** (7787/15185)	53%** (19791/37588)	52%** (15627/29814)	52%** (43205/82587)

Asterisks mark statistical significance, * $p < 0.05$, ** $p < 0.01$.

Table II

Percent Merkel cell carcinomas that present on the left, broken down by age, sex, and body site.

	MCC: % lateralized tumors presenting on the left side			
	scalp & face	**upper limb**	**lower limb**	**Total**
over age 65 - men	54% (266/493)	55%* (236/430)	52% (98/187)	54%** (600/1110)
over age 65 - women	49% (175/357)	58%* (133/230)	54% (131/244)	53% (439/831)
under age 65 - men	53% (31/59)	55% (58/106)	43% (43/100)	50% (132/265)
under age 65 - women	53% (31/59)	48% (38/79)	40% (16/40)	48% (85/178)
Total	52% (503/968)	55%** (465/845)	50% (288/571)	53%** (1256/2384)

Asterisks mark statistical significance, * $p < 0.05$, ** $p < 0.01$.