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Left-Sided Excess in the Laterality of Cutaneous Melanoma

An unequal distribution of cancer laterality, particularly in paired organs, has long been documented and generally thought to be related to asymmetries in organ size or behavioral factors such as handedness.1 Recently in a large series patients with cancers in the left testis, right lung, and left ovary were found

Results. The intraclass correlation coefficients for interassessor agreement were 0.91 for PH3 and 0.89 for Ki67, indicating an excellent level of agreement.6 We found that similar to the correlation with mitotic rate, ROG was significantly associated with the Ki67 score (Spearman rank correlation coefficient, 0.44; P < .001) (Figure 1) and with the PH3 score (Spearman rank correlation coefficient, 0.46; P < .001) (Figure 2).

Comment. Although retrospective recall of events leading up to a diagnosis of melanoma is associated with several potential sources of error,2 clinical history remains the only practical tool to assess the evolution of melanomas from their inception. Herein, we have demonstrated a significant correlation between the patient-recall–based ROG and objective assessments of melanoma proliferation using immunohistochemical markers at the time of excision. One limitation of this comparison is that ROG examines the development of a melanoma over its whole course, whereas immunohistochemical markers examine only the state of proliferation at the time of removal.

These findings provide further evidence for the value of ROG in the clinical assessment of melanoma growth kinetics.

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Figure 1. Scatterplot of the relationship between the Ki67 score and the clinical rate of growth.

Figure 2. Scatterplot of the relationship between phosphorylated-histone H3 (PH3) score and the clinical rate of growth.

Methods. To further evaluate the relationship between ROG and melanoma proliferation, we assessed the correlation of ROG with Ki67, a commonly used marker of cell cycle progression,4 and phosphorylated-histone-H3 (PH3), a sensitive marker of mitosis.5 The methods of assessing Ki67 and PH3 have been described elsewhere.6 In brief, recuts of a representative section within the primary melanoma were used for immunohistochemical staining with both markers, and staining was scored by 2 independent assessors without knowledge of ROG. The Ki67 staining (percentage of staining melanoma cells in the dermis) and the PH3 staining (numbers of staining melanoma cells per millimeters squared in the dermis) were assessed, beginning in the most immunoreactive area. The final score of Ki67 and the final score of PH3 were defined as the mean of scores from the 2 assessors.

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to have a significantly better survival than those with contralateral cancers. Apart from anecdotal assertions and very sparse data that suggest asymmetrical differences in the frequency of cutaneous melanoma and photodamage, melanoma laterality has, to our knowledge, never been specifically studied. Investigation of laterality could thus contribute to a better understanding of cancer etiology and prognosis.

**Methods.** As part of a larger study, the lat. of 2143 first cutaneous melanomas was retrieved and clinically validated using a standardized body chart that allowed unequivocal marking of the location of the lesion. After excluding cases with unspecified laterality (n = 228 [11%]) or those on the midline (n = 254 [12%]), 1661 melanomas diagnosed between 1995 and 2002 in 5 Swiss population-based tumor registries (Neuchâtel, St Gallen/Appenzell, Vaud, Valais, and Ticino) were investigated. Results were expressed as left to right (L/R) ratios and stratified by cancer registration area, sex, age group, and subsite. Exact 2-sided 95% confidence intervals (95% CIs) were computed assuming that laterality was binomially distributed.

**Results.** This series included 890 left-sided and 771 right-sided melanomas, yielding an L/R ratio of 1.15 (95% CI: 1.05-1.27). The excess of left-sided lesions was consistently observed across all populations, sexes, age groups, body site, and categories of Breslow thicknesses (Table), although it only occasionally reached statistical significance. The upper limbs was the site with the greatest left-sided excess (27%). Left to right ratios higher than 1 were systematically found for clinical characteristics such as tumor behavior (invasive and in situ), skin type, and morphological type (data not shown).

**Comment.** This multicentric study suggests a moderate but consistently higher frequency of melanoma on the left side of about 15%. Four main potential explanations were identified and explored: chance finding, recording bias, differential sun exposure, and bilateral asymmetry in the number of melanocytes or tumor biological behavior.

Although chance finding cannot be excluded, we believe it is an unlikely explanation for our observation. The pattern was similar for every variable studied and, for instance, the probability of observing simultaneously an excess L/R ratio in all 5 populations was about 3% (1 in 32). The detailed site was thoroughly cross-validated from textual and pictorial support.  

Two nonmethodological explanations for a left-sided excess of melanoma can be speculated. Traveling in a motor vehicle is probably the only frequent human activity that results in side-specific UV exposure depending on the individual position in the car. Swiss drivers sit on the left side of the car and, until the recent availability of air conditioning, their left arm was more likely to be sun exposed through an open window, particularly in summertime. The largest left-sided excess observed for the upper limbs (an L/R ratio of 1.27, 95% CI: 1.05-1.54, Table) and the greater L/R ratio for men (an L/R ratio of 1.38, P = .02, data not shown) than women (an L/R ratio of 1.18, P = .22, data not shown) at this site supports this assumption and the known greater propensity for men to drive. Reports of a left-sided excess of facial photodamage lesions commensurate with time spent driving in the United States and the commoner occurrence of solar keratoses on the right upper limb among Australian men, where drivers sit on the right side of vehicles, concurred with our findings. This hypothesis, however, only partly explains our results, since it cannot account for the left-sided excess of melanomas observed at other body sites.

Several aspects in embryogenesis occur in asymmetric fashion. An asymmetry in the distribution of melanocytes favoring the left body side might occur when these cells migrate from the neural crest during embryonic development. This assumption could be challenged and eventually supported by investigating the laterality of nonmelanocytic skin cancers from the Vaud Cancer Registry database since L/R ratios computed for squamous and basal cell carcinomas registered over a 10-year period (1995-2004) were 1.03 (1286:1244) and 1.00 (2946:2939), respectively (F.L., oral communication, September 2007). An asymmetric development of the angiolymphatic system might lead to a higher progression of left-sided melanoma, which is compatible with our concomitant increase in L/R ratios and melanoma thickness.

This largest study to date to explore melanoma laterality suggests that an asymmetric, melanocytic distribution or, to a lesser extent, a differential sun exposure are plausible etiological explanations for the observed left-
sided excess of melanomas but not of other types of skin cancers.

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COMMENTS AND OPINIONS

Notice of Duplicate Publication: “Invasive Zygomycosis With a Fatal Outcome” (Arch Dermatol. 2005;141[10]:1211-1213)

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alysis of the article by Abdel-Naser et al1 published in the October 2005 issue of the Archives and twice by Youssef et al2,3 shows that information regarding case 1, a 24-year-old man, and case 2, a 9-year-old boy, was previously published both in print2 and online3 at the time that the Archives published the manuscript. The Archives received the manuscript on June 21, 2004, gave provisional acceptance on Dec 26, 2004, and final acceptance on May 5, 2005. The authors had ample opportunity to amend the manuscript to cite the prior publication of the case in September 2004 in print2 prior to our publishing it in October 2005, and to cite online3 in June 2005 the acceptance of the manuscript by the Archives.

The first publication of the cases was as part of a series of cases including 5 adults and 1 child who were seen at the Dermatology and Venerology Ear, Nose, and Throat Departments at Ain Shams University, Cairo, Egypt, from 2002 through 2004.2 In this instance, the authors Youssef and El-Fakar should have informed their co-author Abdel-Naser, who was the corresponding author for the Archives article and was not an author on the prior publications, that the cases of the child and the 24-year-old man were part of the retrospective study. Abdel-Naser could have amended the manuscript at the time of our request for revision in December 2004 to cite the prior publication in September 2004.2

“Prior publication” means publication in any language and any medium, and authors have an obligation to cite and disclose to the Archives editor—if not “overdisclose”—every venue or channel in which the same or substantially similar information was published in the past. This enables the editor to decide what is new, accurate, relevant, and worthy of publication in the Archives. Authors must realize that the Authorship Responsibility Forms they complete, sign, and submit to the editor are important documents of editorial, legal, and ethical consequence. The forms contain statements and representations upon which we rely, and trust to be accurate, that are made in good faith. Our readers expect that, as well.

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VIGNETTES

Metastatic Melanoma of the Tongue Arising From Oral Melanosis

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rimary oral melanoma is a rare tumor that has been estimated to represent 0.1% of melanoma cases in whites.1 A review of 20 cases of tongue melano-

momas1 and a literature survey in PubMed revealed a total of 32 published cases. One-third of patients diagnosed as having primary oral melanoma also had preexisting pigmented lesions at the same site. The prognosis is poor, with a 3-year survival rate of only 26.4%.6 We report a lethal case of primary melanoma of the tongue that developed within an oral melanosis that had been biopsied 9 years before its malignant transformation.

Report of a Case. A 57-year-old man without a family history of melanoma presented in February 1993 with