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Testing the Divergent Pathway Model for Melanoma

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Abstract

Post hoc analysis of a large US population-based study of melanoma was carried out to test Whiteman's divergent pathway model that suggests different etiologic pathways for melanoma based on (1) pattern of sun exposure, as characterized by anatomic site, and (2) host factors such as propensity for melanocyte proliferation, as characterized by nevus status. Study subjects consisted of 528 newly diagnosed cases of melanoma among Caucasian residents of Connecticut. Nurse-interviewers obtained information on age, gender, hair color, eye color, skin color, history of sun exposure, history of painful sunburns, anatomic site of melanoma, and number of nevi on both arms and the back. Age-adjusted simultaneous odds ratios with 95% confidence intervals were generated using nevus status as the dependent variable. The study found a statistically significant relationship ($p<0.01$) exists between anatomic site of melanoma and having many nevi. This is consistent with the prediction of the divergent pathway model for different paths to melanoma formation based on pattern of sun exposure and host propensity for melanocyte proliferation. Further investigation into the biological basis for the divergent pathway is warranted so that skin cancer prevention strategies can be tailored to specific populations.

Introduction

Cutaneous malignant melanoma, a tumor arising from melanocytes, is by far the most common fatal skin cancer (1). It is the fifth most common cancer among men and the seventh most common cancer among women in the United States (2). Moreover, the incidence of melanoma is rising more rapidly than that of any other cancer: the frequency of melanoma has increased by a factor of 15 in the last 60 years (3).

Sun exposure is generally accepted as a major causative factor behind melanoma (5). However, the relationship is complex, as illustrated by apparent paradoxes in melanoma epidemiology. The prevalence of melanoma in susceptible populations has long been known to vary inversely with latitude of residence (6), yet measures of individual sun exposure have been inconsistently associated with melanoma (7). Indoor workers have a higher risk of melanoma than outdoor workers (8). Furthermore, a small proportion of melanomas arise in sites that are completely protected from the sun, such as the axillae (9). In sum, while pattern of sun exposure is recognized as an important determinant of melanoma, no consistent signature of ultraviolet exposure has been found in any gene mutated in melanoma and thus mechanisms mediated by processes other than direct absorption of ultraviolet light by DNA may contribute to progression to melanoma (10).

Differences in melanoma incidence and age-at-onset have been observed across anatomic site. These differences defy explanation based upon the pattern of sun exposure alone, i.e. chronic versus intermittent (11). It has therefore been

suggested that the response of melanocytes to ultraviolet light varies depending on their location in the body (12).

Collectively, the evidence points to melanomas arising along distinct genetic pathways via a complex interaction of factors related to anatomy, heredity, and sun exposure (10). The recently proposed 'divergent pathway' model for development of cutaneous melanoma seeks to offer a unifying hypothesis for all of the epidemiologic and experimental data on melanoma (13). It proposes two different pathways for the development of melanoma. In the first pathway, individuals with a low propensity for melanocyte proliferation, as characterized by a low nevus count, develop melanoma after chronic exposure to the sun. Hence, melanomas arising in these individuals will occur predominantly on habitually sun-exposed anatomic sites, such as the head, neck, and arms. In the second pathway, melanoma develops in individuals with a high propensity for melanocyte proliferation, as characterized by a high nevus count. In this group, sun exposure plus host factors leads to melanoma formation in intermittently-exposed anatomic sites, such as the trunk.

The aim of the present study was to conduct *post hoc* analysis of a large, population-based case-control study of invasive malignant melanoma in Connecticut residents from 1987-1989 to query whether melanoma characteristics and risk factors differ across anatomic site as predicted by the 'divergent pathway' model.

Results

The demographic characteristics and histologic subtypes of the subjects are presented in Table 1.Age-adjusted simultaneous odds ratios with 95% confidence intervals were generated using nevus status as the dependent variable and are presented in Table 2. Anatomic site of melanoma predicted a high nevus count, with $p<0.01$. Melanomas in chronically sun-exposed sites predicted lower nevus count (95% CI 0.26 – 0.85), while melanomas in intermittently sun-exposed sites such as the upper shoulder and back, lower back, chest and stomach had 95% CI overlapping with one.

Melanoma among males achieved a statistically significant associated with high nevus count (95% CI 1.07 – 2.39). No history of painful sunburns was also predictive of a high nevus count (95% CI 1.01 – 2.26). No other demographic characteristics or histologic subtypes were statistically significantly associated with high nevus count.

Table 1. Demographic characteristics and histologic subtypes

Variable	Melanoma in chronically sun-exposed site	Melanoma in intermittently sun-exposed site
Sex:		
Male	50	238
Female	35	225
Age		
< 45	14	140
45 - 64	32	191
65+	39	133

Histologic subtype:		
Lentigo maligna	49	33
Nodular	5	52
Superficial spreading	17	316
Other	13	54

Table 2. Multivariate age-adjusted Odds Ratios with 95% Confidence Intervals for nevus count

Variable	Odds Ratio*	95% CI	P-Value
Anatomic site of melanoma:			0.006
Head, face, and neck	0.47	0.26 – 0.85	
Upper shoulder and back	1.13	0.68 – 1.87	
Lower back	1.53	0.72 – 3.26	
Chest and stomach	0.77	0.39 – 1.52	
Male gender	1.60	1.07 – 2.39	0.02
No history of painful sunburns	1.51	1.01 – 2.26	0.04

*Age-adjusted odds ratio

Discussion

The study found a statistically significant relationship ($p<0.01$) exists between anatomic site of melanoma and having many nevi. This is consistent with the prediction of the divergent pathway model for different paths to melanoma formation based on pattern of sun exposure and host propensity for melanocyte proliferation. However, nevus count was unable to predict anatomic site of melanoma ($p<.06$, unpublished results), which argues against clinical

significance. The association between male gender and no history of painful sunburns with high nevus counts is not surprising given that males who develop melanoma have higher nevus counts.

Given the finding that individuals with higher nevus counts are associated with anatomic site of melanoma, it may be that high nevus count is indicative of melanocyte instability. This could place individuals with unstable melanocytes at higher risk for development of melanoma as a result of intermittent sun exposure. On the other hand, individuals with stable melanocytes, as demonstrated by low nevus counts, are protected against this pathway of melanoma. They are susceptible to development of melanoma on chronically sun-exposed sites, such as the head, face, and neck. Further investigation into the biological basis for the divergent pathway is warranted so that skin cancer prevention strategies can be tailored to specific populations.

Materials and Methods

Cases for this study were obtained as previously described (14). Briefly, subjects consisted of newly diagnosed cases of melanoma among Caucasian residents of Connecticut between 1987 and 1989 as identified by the tumor registry. Nurse-interviewers obtained information on age, gender, hair color, eye color, skin color, history of sun exposure, history of painful sunburns, anatomic site of melanoma, and number of nevi on both arms and the back. Pathologists examined specimens and determined the histologic subtype of each melanoma. Age-adjusted simultaneous odds ratios with 95% confidence intervals were

generated using nevus status as the dependent variable. A high nevus count was defined as having more than eleven nevi counted on both arms and the back.

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