(1997) DQB1*0202 and the new DQB1*0203 allele: a fourth pair of DQB1 alleles differing only at codon 57. *Tissue Antigens* 49:271–3

Price VH, Colombe BW (1996) Heritable factors distinguish two types of alopecia areata. *Dermatol Clin* 14:679–89

Smikie MF, Pascoe RW, Barton E, Morgan O, Christian N, Dowe G *et al.* (2001) HLA-DRB3*0101 is associated with Graves' disease in Jamaicans. *Clin Endocrinol (Oxf)* 55:805–8

Wang SJ, Shohat T, Vadheim C, Shellow W, Edwards J, Rotter JI (1994) Increased risk for type I (insulin-dependent) diabetes in relatives of patients with alopecia areata (AA). *Am J Med Genet* 51:234–9

Welsh EA, Clark HH, Epstein SZ, Reveille JD, Duvic M (1994) Human leukocyte antigen-DQB1*03 alleles are associated with alopecia areata. *J Invest Dermatol* 103:758–63

Epidemiologic Support for Melanoma Heterogeneity Using the Surveillance, Epidemiology, and End Results Program

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TO THE EDITOR

Several studies have used evidence evaluating genetic alterations (Curtin *et al.*, 2005) and anatomic location (Whiteman *et al.*, 2003) to support theories that melanoma is a heterogeneous disease with differing etiologies. Using data from the large-scale, population-based Surveillance, Epidemiology, and End Results Program (SEER) of the National Cancer Institute, we examined whether age-specific incidence patterns separated by sex and site would reveal distinct melanoma subgroups.

Age, sex, and anatomic site were abstracted for all microscopically confirmed, first invasive cutaneous melanomas among non-Hispanic white adults collected by the SEER 17 Registry Program from 2000 to 2004. Incidence rates, summarized across 5-year age groups, were plotted by age at diagnosis on a log-log scale, and age distribution curves were created. Detailed materials and methods are available in Supplementary Materials and Methods.

After excluding 15 cases missing age at diagnosis, 48,673 cases were available for analysis (Table 1). Fifty-six percent of patients were male, and the mean age at diagnosis was 57.0 years. Forty-one percent of all melanomas occurred among those 40–59 years of age. However, the age-specific incidence rate peaked among people aged 70–79 years, who had an incidence rate 5.9 times higher (95% confidence intervals, 5.6–6.2) than those aged 20–29 years. The incidence rate ratio for females compared to males was 0.7 (95% confidence intervals, 0.7–0.7). Forty-three percent of melanomas were located on the extremities, 34% on the trunk, 12% on the face/ears, 7% on the scalp/neck, and 4% at other/unclassified sites.

The age-specific incidence rate curve and the age distribution for all melanoma cases are shown in Figure 1. Rates for all cases increased rapidly until age 55–59, then continued to rise at slower rates before beginning to decline (Figure 1a). The age distribution plot displayed a multimodal distribution, with distinct

Table 1. Frequency and incidence of invasive cutaneous melanoma in non-Hispanic white adults collected by SEER-17 from 2000 to 2004[1] (*n*=48,673)

Characteristic	*n* (%)[2]	Incidence rate per 100,000 (SE)	Incidence rate ratio (95% CI)[3]
Age at diagnosis (years)			
Mean+SD	57.0 (16.6)	NA	NA
Age groups (years)			
20–29	2,391 (5)	9.1 (0.2)	1
30–39	5,188 (11)	16.2 (0.2)	1.8 (1.7–1.9)
40–49	9,376 (19)	25.5 (0.3)	2.8 (2.7–2.9)
50–59	10,585 (22)	35.5 (0.3)	3.9 (3.7–4.1)
60–69	8,541 (18)	46.5 (0.5)	5.1 (4.9–5.4)
70–79	7,769 (16)	53.3 (0.6)	5.9 (5.6–6.2)
80+	4,823 (10)	49.6 (0.7)	5.5 (5.2–5.7)
Sex			
Male	27,300 (56)	33.6 (0.2)	1
Female	21,373 (44)	24.7 (0.2)	0.7 (0.7–0.7)
Anatomic site			
Extremities	21,008 (43)	12.5 (0.1)	1
Trunk	16,610 (34)	9.9 (0.1)	0.8 (0.8–0.8)
Face/ears	5,875 (12)	3.5 (<0.01)	0.3 (0.3–0.3)
Scalp/neck	3,300 (7)	2.0 (<0.01)	0.2 (0.2–0.2)
Other/unclassified	1,880 (4)	1.1 (<0.01)	0.1 (0.1–0.1)

CI, confidence interval; SD, standard deviation; SE, standard error; SEER, Surveillance, Epidemiology, and End Results; NA, not applicable.
[1]Note: 15 cases were excluded for missing age at diagnosis.
[2]Percentages are rounded and may not sum to 100.
[3]Rate ratios compare rates for given characteristics to a referent characteristic with an assigned rate ratio of 1.0.

Abbreviations: SEER, Surveillance, Epidemiology, and End Results

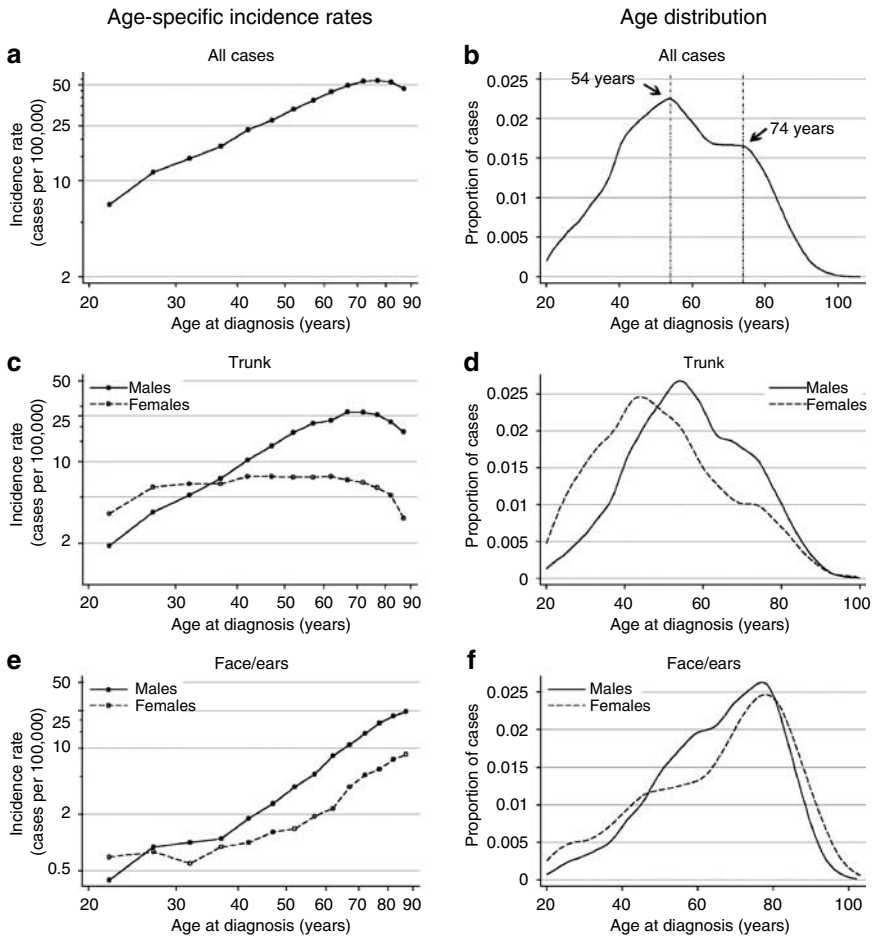

Figure 1. Age-specific incidence rates and age distribution of melanoma. Age-specific incidence rates per 100,000 population of invasive melanoma are shown for (**a**) all cases, (**c**) trunk melanomas, and (**e**) face/ear melanomas. Age distributions are shown for (**b**) all cases, (**d**) trunk melanomas, and (**f**) face/ear melanomas; the vertical axis represents smoothed estimates of the proportion of patients who developed melanoma at the corresponding age at diagnosis on the horizontal axis. Rates and distribution curves are depicted in solid lines for males and in dashed lines for females.

early-onset and late-onset peak frequencies of melanoma occurring at ages 54 and 74 years, respectively (Figure 1b).

Melanomas demonstrated different incidence patterns by anatomic site. Age-specific incidence rates among those with trunk melanoma generally increased until age 55–59 years, then plateaued and subsequently declined (Figure 1c). The flattening of rates for trunk melanoma occurred earlier and was more extreme for females than for males. The age distribution of trunk melanoma was predominantly unimodal, with early-onset peak frequencies occurring at age 54 for males and 44 for females (Figure 1d). In contrast, age-specific incidence rates among those with face/ear melanoma increased sharply throughout older age (Figure 1e). The age distribution for face/ear melanoma was unimodal with late-onset peaks at age 77 for males and at age 78 for females (Figure 1f). Incidence rates for melanomas of the extremities, scalp/neck, and other/unclassified sites demonstrated various mixtures of these two patterns and did not show unimodal distributions (data not shown). These distinct patterns for trunk and face/ear melanomas were maintained when the analysis was limited to those classified as superficial spreading melanoma and nodular melanoma histological subtypes (Figure 2).

The multimodal distribution of invasive melanoma might be explained, in part, by divergent patterns for anatomic site. Broken down by site, trunk melanomas displayed an early-onset peak of melanoma incidence, while face/ear melanomas demonstrated a late-onset incidence peak. Comparable divergent incidence rate patterns have been noted for breast cancer, and the bend in age-specific rates near menopause has been termed Clemmesen's hook (Clemmesen, 1948; Anderson *et al.*, 2005). Clemmesen's hook on the age-specific incidence rate curve has been shown to correspond to the dip between the bimodal peaks of the age distribution plot (Anderson *et al.*, 1950). Our data suggest the existence of a Clemmesen's hook for melanoma.

Bulliard (2000) analyzed age-and surface area-adjusted incidence rates by anatomic site for the non-Maori population of New Zealand using data from 1968 to 1993 and found patterns similar to ours. Elwood and Gallagher (1998) examined site-specific incidence rates per unit area of skin for 1,033 patients in a Canadian melanoma registry and noted that the density of melanoma on the back exceeded that of the face before age 50, but that melanoma density was greatest on the face at later ages. Additionally, Dennis (1999) used SEER data collected during 1972–1994 to examine age-specific incidence curves by site adjusted for birth-cohort effects. While adjusting for birth-cohort increased incidence rates for all sites, especially after age 50, the incidence patterns for trunk and head resembled those we found for trunk and face/ears.

Divergent age-specific incidence patterns support hypotheses that melanomas may emerge from more than one causal pathway and complement recent evidence identifying distinct melanoma genotypes. Whiteman *et al.* (2003) have proposed a ''divergent pathway'' model in which people with inherently low propensity for melanocyte proliferation require chronic sun exposure to habitually exposed sites, such as the face, to develop melanoma, whereas people with a high propensity for melanocyte proliferation develop melanomas on sites with unstable melanocytes, such as the trunk, with less or intermittent solar damage. Our data support this model by displaying an early-onset peak frequency for trunk melanomas and a late-onset peak frequency for face/ear melanomas. Additionally,

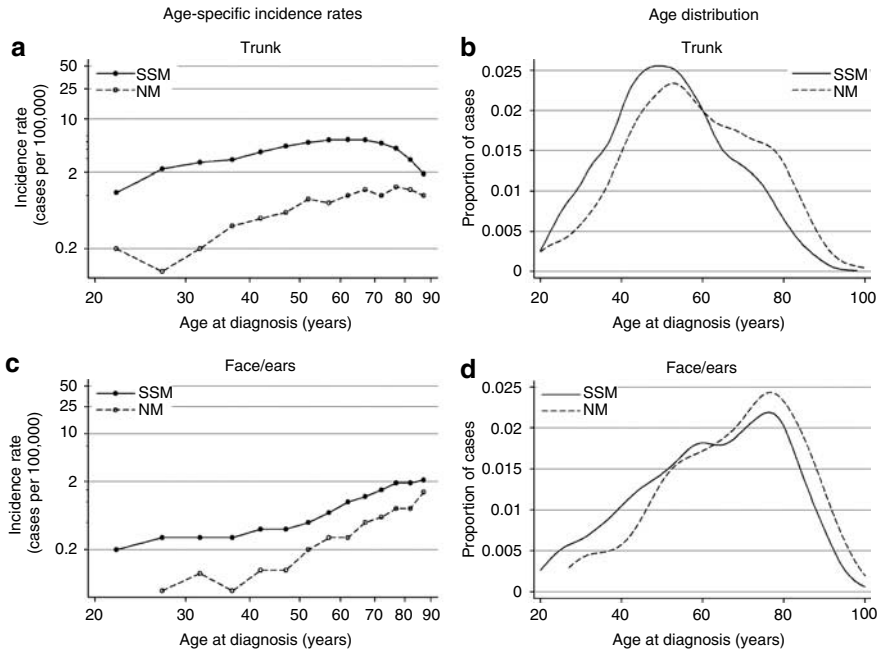

Figure 2. Age-specific incidence rates and age distributions by site and by histological subtype. Age-specific incidence rates per 100,000 population of invasive superficial spreading (SSM) and invasive nodular melanoma (NM) are shown for (**a**) trunk and (**c**) face/ear locations. Age distributions of SSM and NM at (**b**) trunk and (**d**) face/ear locations are also shown. No cases of NM on the face/ears were collected for the age group 20–24 years. Rates and distribution curves are depicted in solid lines for SSM and in dashed lines for NM.

BRAF mutations, found in 20–80% of cutaneous melanomas (Lang and MacKie, 2005), occur more frequently in melanomas of patients <50 years of age and are positively associated with truncal location (Liu *et al.*, 2007; Thomas *et al.*, 2007). *BRAF* mutations are also significantly more likely to be found in melanomas on skin without evidence of chronic sun damage, as reflected by the lack of severe histological solar elastosis (Maldonado *et al.*, 2003; Curtin *et al.*, 2005). Thus, our epidemiologic incidence patterns match what is already known about one genetically distinct type of melanoma.

Other evidence suggests that histological growth patterns may be useful in identifying melanoma subtypes that have distinctive biological behaviors (Clark *et al.*, 1969). It is well-known that lentigo maligna melanoma, a subtype associated with cumulative sun exposure, frequently occurs on the head and neck in older adults (Cohen, 1995). Nevertheless, when our analysis was limited to melanomas classified as superficial spreading or nodular melanoma subtypes, the patterns by site persisted.

Our analysis demonstrates the value of using a large-scale, population-based database for hypothesis-generating and hypothesis-testing. Melanoma is a heterogeneous cancer and is likely to represent tumors with multiple etiologies and perhaps different outcomes. Further research on the genetic make-up of distinct phenotypes will advance our understanding of melanoma and may improve our ability to prevent and treat this disease.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Materials and Methods.

REFERENCES

Anderson E, Reed SC, Huseby RA, Oliver CP (1950) Possible relationship between menopause and age at onset of breast cancer. *Cancer* 3:410–4

Anderson WF, Jatoi I, Devesa SS (2005) Distinct breast cancer incidence and prognostic patterns in the NCI's SEER program: suggesting a possible link between etiology and outcome. *Breast Cancer Res Treat* 90:127–37

Bulliard J (2000) Site-specific risk of cutaneous malignant melanoma and pattern of sun exposure in New Zealand. *Int J Cancer* 85:627–32

Clark WH, From L, Bernardino EA, Mihm MC (1969) The histogenesis and biological behavior of primary human malignant melanomas of the skin. *Cancer Res* 29:705–27

Clemmesen J (1948) Carcinoma of the breast—Symposium. I. Results from statistical research. *Br J Radiol* 21:583–90

Cohen LM (1995) Lentigo maligna and lentigo maligna melanoma. *J Am Acad Dermatol* 33:923–36

Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H *et al.* (2005) Distinct sets of genetic alterations in melanoma. *N Engl J Med* 353:2135–47

Dennis LK (1999) Melanoma incidence by body site: effects of birth-cohort adjustment. *Arch Dermatol* 135:1553–4

Elwood JM, Gallagher RP (1998) Body site distribution of cutaneous malignant melanoma in relationship to patterns of sun exposure. *Int J Cancer* 78:276–80

Lang J, MacKie RM (2005) Prevalence of exon 15 BRAF mutations in primary melanoma of the superficial spreading, nodular, acral, and lentigo maligna subtypes. *J Invest Dermatol* 125:575–9

Liu W, Kelly JW, Trivett M, Murray WK, Dowling JP, Wolfe R *et al.* (2007) Distinct clinical and pathological features are associated with the $BRAF^{T1799A(V600E)}$ mutation in primary melanoma. *J Invest Dermatol* 127:900–5

Maldonado JL, Fridlyand J, Patel H, Jain AN, Busam K, Kageshita T *et al.* (2003) Determinants of BRAF mutations in primary melanomas. *J Natl Cancer Inst* 95:1878–80

Thomas NE, Edmiston SN, Alexander A, Millikan RC, Groben PA, Hao H *et al.* (2007) Number of nevi and early life ambient UV exposure are associated with BRAF-mutant melanoma. *Cancer Epidemiol Biomarkers Prev* 16:991–7

Whiteman DC, Watt P, Purdie DM, Hughes MC, Hayward NK, Green AC (2003) Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. *J Natl Cancer Inst* 95:806–12