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Malignant melanoma risk by nativity, place of residence at diagnosis, and age at migration

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Although geographic latitude is clearly linked to the risk of cutaneous malignant melanoma, the chronology of this link is unclear. Based on the 4,611 cases of melanoma with known place of nativity diagnosed in 1972-82 among the non-Latino White residents of Los Angeles County (California, United States) of known place of origin, migrants to Los Angeles from higher US latitudes enjoy relative safety from skin melanoma. This relative safety is largely unaffected by the interval since migration, even after decades of residence in Los Angeles. The same relative protection is enjoyed by native residents of more northerly US communities in comparison with co-resident migrants from the southwestern US. While the observed effect of latitude is consistent with the accepted importance of solar radiation as a determinant of melanoma risk, it suggests that early, rather than late or cumulative, exposure is of most importance. This finding does not affirm the belief that protection of adult skin from exposure to the sun will reduce the risk from melanoma. It does suggest that decades must pass before it will be possible to assess the impact on melanoma risk of any increase in ultraviolet radiation delivered to the earth as a result of the destruction of atmospheric ozone.

Key words: Latent period, latitude, melanoma, migration, solar exposure, United States.

Introduction

Low geographic latitude is linked to cutaneous malignant melanoma mortality[1,2] and incidence,[3,4] presumably by means of solar radiation to the skin,[5] and underlies the prevailing recommendation[6] that excess direct sunlight be avoided. Latitude, however, is an inadequate explanation for the geographic distribution of melanomas,[7-10] and the anatomic site distribution of melanomas varies by latitude[11] and social class,[12] following neither the distribution of unprotected skin nor that of other sun-induced skin cancers.[13] In part, these anomalies must reflect variations in sun-related behavior, and an assessment of behavior requires an understanding of the time-frame of the pertinent exposure. While detailed personal recollections of exposure can be recorded in case-control studies, they are very diverse and therefore expensive to collect in sufficient numbers. However, documentation of the lifetime changes in latitude of residence can be obtained in simple, objective, and chronologically specific form, with little postdiagnosis bias, on thousands of cases and unaffected subjects. We previously reported such a link between place of nativity and melanoma risk,[14] and now present a more detailed description.

The White population of Los Angeles County

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(LAC) resides at a low United States latitude, and receives medical care of homogeneous quality. A majority of current long-term residents were born in less sunny places. Moreover, many California natives themselves have migrated to more northerly locales. Internal migration is commonplace in the US for persons of all backgrounds, and those who change their address in America are more comparable to their old and new neighbors than are international migrants.

Materials and methods

The Los Angeles Cancer Surveillance Program identifies each county (subdivisions of states) resident for whom any cancer (other than squamous- and basal-cell skin cancer) is verified microscopically or recorded on a death certificate.[14] Melanomas constitute roughly two percent of these diagnoses, and it is estimated that ascertainment of them is at least 96 percent complete. Using the pathology record, each reported neoplasm is classified according to morphology and anatomic site, and each registered patient is characterized on the basis of date and place (state) of birth, sex, race, occupation, residential address, and social security number (SSN). Address is used to determine socioeconomic category, based on the aggregation of 1970 US residential census tracts according to household median income and mean education. The SSN is a unique number which is assigned to US residents at or before entry into the work force or tax roll;[15] one component of the SSN indicates the State of issue. Surnames are assigned to ethnic categories based on etymology, local ethnic and genealogic resources, and an updated and augmented version of the 1970 US census list of Spanish surnames.[16] Age, sex, and race-specific population estimates for each year of incidence were prepared using the 1970 and 1980 census returns, with standard adjustments for intercensus population trends, variations in the census criteria for Latino heritage, and race-specific undercounting. An annual age-adjusted incidence rate (AAIR) for each major racial group in LAC over the period of interest was calculated on the basis of patients of known race although a disproportionate number of malignant melanoma patients are identified from less complete outpatient records which do not specify race. Because more than 96 percent of all Los Angeles melanoma patients of known race are non-Latino Whites—the group with easiest access to private outpatient care—we have calculated a second AAIR based on the presumption that patients of unknown race are non-Latino Whites.

Because some hospitals now have ceased to record the birthplace of patients, analysis of nativity was confined to patients diagnosed in 1972-82, when birthplace was recorded for roughly 80 percent of all patients, and all conclusions about birthplace were based only on patients of known birthplace. In Los Angeles, non-Latino Whites neither choose a place of residence nor seek medical care in any systematic relation to their US birthplace. Most LAC residents who are native Californians grew up in southern California. In order to identify the other residents who were exposed to a high level of daily solar radiation in childhood, we sought to identify the other places with such exposure using the USESSA (now NOAA) Climatic Atlas of the United States,[17] setting an arbitrary threshold of 450 Langleys. Of the five other states with longstanding major population centers meeting that criterion, two (Nevada and Florida) contribute few migrants to LAC, and the migrants from two others (New Mexico and Hawaii) are not numerous and include a disproportionately large number of dark-skinned low-risk Whites.[18,19] The remaining state, Arizona, contains a White population known to be at high risk,[20] and contributes a substantial number of migrants to LAC. California and Arizona therefore were designated as places of intense childhood exposure, and on that basis we twice divided all cancer cases of known birthplace, first according to nativity, and then using that portion of the SSN which indicates the state of issuance. One of the four resulting subgroups contains Los Angeles residents who are lifetime residents of California and/or Arizona (CA/AZ), and a second contains those interstate immigrants (inmigrants) to southern California, born mostly in midwestern, eastern, or south-central states who received their SSNs after arrival in California or Arizona, indicating probable migration before their late teens and certainly before the end of their third decade of life. For the oldest patients in this group, migration may have occurred later, but still took place before the appearance of the Social Security Administration in 1936. A third group is composed of inmigrants, generally from those same regions of the country, who received SSNs before migration, and the final group contains the few CA/AZ natives who are now Los Angeles residents but who received their SSNs elsewhere.

The census does not provide detailed population estimates by nativity, ethnicity, or place of SSN issuance. We therefore compared these subsets by computing proportional incidence ratios (PIRs) in the conventional way, using as a standard the age-specific frequency of all other cancer diagnoses. This method requires the assumption that age-specific incidence of nonmelanoma cancers is relatively constant from subset to subset. This assumption holds for geographically diverse US populations. The annual, age-adjusted, all-

sites incidence rates for Los Angeles Whites—a majority of whom are inmigrants—are essentially identical to those for Whites in other US registry areas;[11,21] this suggests that internal migration is independent of all-sites cancer risk. Moreover, rough all-sites rates for each sex-specific age group of 1977-83 Los Angeles White residents, by nativity, can be computed using self-designated non-Latino population estimates from the 1980 census public-use sample, adjusting for the age and sex-specific proportion of cases of unknown birthplace. The all-sites rate for the California-born population was within five percent of that for the analogous inmigrant group for five of the 12 sex-specific 10-year age groups between 14 and 75, within 15 percent for another five, and within 25 percent for the other two.

We first compared the proportional risk of melanoma according to nativity alone, and then according to nativity and place of SSN issuance. A likelihood ratio (chi-square with one degree of freedom) was used to compute 95 percent confidence intervals (CI) for each estimate of PIR.[22] Analogous comparisons of melanoma incidence were made for more northerly US residential populations. From the Seattle-Puget Sound Cancer Surveillance System, we obtained frequencies of malignant melanoma cases (2,611) and of all other cancer cases (102,300) by age and sex for 1974-83 (cases in that registry are 93 percent White) according to nativity and place of SSN issue. SEER Program[21] staff provided us with the 1973-82 frequencies of malignant melanoma (16,757) and of other cancers (750,061) in Whites by age, sex, and nativity from the San Francisco-Oakland Bay Area population-based cancer registry and from the combined other SEER registries, excluding Seattle and San Francisco. The proportional comparisons between risk in natives and in inmigrants for the other geographic areas were made in the manner described above.

Analogous frequencies were obtained for deaths from a file of US mortality by age, sex, race, cause, state of birth, and place of death for 1979-81. Proportional mortality ratios for melanoma were derived using mortality from all other causes, rather than other cancers, as the referent standard.

Most interstate migration in the US in this century has taken place before the age of 30,[23] which suggests that most middle-aged or older inmigrants have resided in Los Angeles for decades. To confirm that, for each 10-year birth cohort, we used decennial (1890 through 1980) census enumerations of LAC domestic inmigrants to track the growth in size of each residential inmigrant cohort up to the time of diagnosis.[24] From this array, and from cohort-specific distributions of age at SSN issuance obtained from the Social Security Administration, we estimated the median interval between melanoma diagnosis and inmigration or SSN issuance for each residential cohort.

Results

Of the 392,322 reported cancer diagnoses made in Los Angeles during the period 1972-82, 8,520 were of malignant melanoma in Whites or Blacks. Average, annual, age-adjusted incidence rates by race for this registry and other US population-based cancer registries for roughly the same period are presented in Table 1. The protection afforded those with darker skin pigmentation[18,25] is evident in Los Angeles. The proportion of SEER patients of undetermined race over this period is small (about two percent),[26] and the more appropriate Los Angeles rate to use for comparison is that based on the inclusion of cases of unknown race. The rates of melanoma in Los Angeles White men and women are nearly twice as high as the nationwide rates in the same period.

The remaining analysis is restricted to melanomas known to be diagnosed in non-Latino Whites. Of the 6,515 such cases, birthplace was available for 4,611. In Table 2, age-standardized proportional risk from melanoma is shown by state of birth. Male and female residents of Los Angeles County born in CA/AZ have a roughly 60 percent increased risk in comparison with residents who were born elsewhere. None of the 12 gender-specific, 10-year-age-specific PIRs between 14 and 75 was below 100, and only one was under 130; for eight of the 12, the 95 percent CI excluded 100.

In Seattle, the same pattern of risk by nativity is seen, even though the absolute incidence is roughly half of that in Los Angeles, and the high-risk natives of lower latitudes are inmigrants and not stay-at-homes (SEER referent). In the San Francisco Bay area, the effect of CA/AZ nativity is consistently present, but the contrast is less strong than in either Los Angeles or Seattle; this might be expected because most native Californians in the Bay area grew up in sunlight more similar to that in northern US states than to that in southern California. CA/AZ natives living in the other areas of the country contrast more strongly with their co-residents than in Los Angeles or Seattle, presumably because the baseline risk in these areas is lower. The mortality comparisons are nearly identical to those based on incidence. No matter where they reside, men and women from the southwest seem to be at half-again the risk of neighbors born farther north.

In Table 3, those Los Angeles residents who migrated south in time to be assigned CA/AZ SSNs can be seen to have a level of risk only somewhat higher than those who migrated as adults. Surprisingly, this seems to be true even for Seattle residents who had

Table 1. Average, annual age-adjusted[a] incidence rate per 10^5 (AAIR) for cutaneous malignant melanoma by residence and race: selected US populations

Population	Males		Females	
	AAIR	No.	AAIR	No.
Los Angeles County, 1972-82				
Blacks	1.1	30	1.0	34
Latinos[b]	3.3	124	3.6	172
Other Whites[c]	12.1	3,333	10.0	3,182
All other Whites[d]	15.3	4,107	12.4	4,053
SEER registries, 1973-81				
Black	0.9	48		51
Whites, total[e]	8.2	6,249	7.2	6,248
Connecticut	8.8	1,146	7.2	1,088
Detroit	6.5	905	5.0	812
Iowa	6.2	790	6.1	916
Atlanta[f]	10.9	358	9.5	380
New Mexico[g]	11.1	331	10.9	359
Utah	7.9	363	7.4	395
Seattle-Puget Sound[h]	7.5	624	7.0	631
San Francisco-Oakland	10.3	1,244	9.0	1,240
Hawaii	21.9	246	14.9	178

[a] 1970 US census age-distribution standard.
[b] Spanish-surnamed.
[c] Non-Latino Whites excluding cases of unknown race.
[d] Non-Latino Whites including cases of unknown race.
[e] Including Latinos, except in New Mexico.
[f] 1975-79.
[g] 'Angelos' (non-Latino, non-Black, non-Indian).
[h] 1974-80.

passed through the southwest only at the time of SSN issuance. In each case, the age-standardized rate is representative of the age-specific rates.

Inmigrant risk in Los Angeles was examined in relation to the characteristics of the tumor at diagnosis. The PIRs were elevated uniformly for melanomas of the face and forearms ($n = 577$); the scalp, neck, back and shoulder ($n = 1{,}571$); the chest, abdomen, hip, and thigh ($n = 709$); the upper arm ($n = 867$); and the leg and foot ($n = 437$).

A strong effect of birthplace can be seen in Table 4 for superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM), and especially nodular melanoma (NM). PIRs for NM in each gender lie outside the age-adjusted confidence intervals for SSM. The link to early, rather than late migration was also generally present for each subgroup, but weaker for NM than for the other types. Tumor thickness was not generally available, but nativity and early migration effects were similar for localized and nonlocalized melanoma. No migration gradient was evident in Los Angeles for either ocular melanoma or the few melanomas of other noncutaneous origin.

Inmigrants in cohorts born before 1910, which include all study subjects diagnosed after age 60, usually had arrived in Los Angeles by 1930, more than 50 years before the diagnosis (Table 5). Most of the study subjects in cohorts born before 1945, including those diagnosed between ages 30 and 60, had arrived more than 20 years previously. Any inmigrant patient with a California SSN diagnosed after age 50 is likely to have arrived in California more than 40 years before the diagnosis.

Figure 1 describes the age trend in PIR according to nativity and place of residence; the referent in this and succeeding figures is the SEER age-specific proportional incidence in persons neither born nor resident in CA/AZ. Los Angeles resident inmigrants younger than age 25 (men) or 35 (women), most of whom probably arrived in Los Angeles as children, are at a high risk comparable to that of natives. Older CA/AZ natives, whether current residents of Los Angeles or not, have a risk two to three times that of their neighbors. In men, the gradient drops in the oldest age group, but the drop follows upon a peak in the previous group.

In Figure 2, the duration of the increase in age-specific risk conferred by an early childhood in Los Angeles is evaluated by comparing the age-specific risk for CA/AZ natives to that for childhood (pre-workforce)

Table 2. Age-adjusted proportional incidence/mortality ratio (PIR/PMR) of cutaneous malignant melanoma among non-Latino Whites by residence and nativity

Residence nativity	Males			Females		
	PIR/PMR	CI[a]	No.	PIR/PMR	CI[a]	No.
			Incidence			
Los Angeles County, 1972, 82[b]						
CA/AZ	166	151-182	667	155	141-171	644
Other	100	—	1,742	100	—	1,558
Seattle-Puget Sound, 1974-83						
CA/AZ	161	127-201	72	141	110-179	68
Other	100	—	924	100	—	994
San Francisco-Oakland, 1973-82						
CA/AZ	122	106-141	317	115	199-133	294
Other	100	—	472	100	—	428
Other SEER Registries,[c] 1973-82						
CA/AZ	251	205-303	87	198	154-249	64
Other	100	—	3,066	100	—	2,870
			Mortality			
California and Arizona, 1979-81						
CA/AZ	146	128-167	337	137	115-163	201
Other	100	—	741	100	—	447
Other states, 1979-81						
CA/AZ	166	113-204	86	136	101-177	50
Other	100	—	7,302	100	—	5,269

[a] CI = 95% confidence interval.
[b] Excluding Latinos.
[c] Connecticut, Detroit, Hawaii, Iowa, New Mexico, Utah, Atlanta.

Table 3. Age-adjusted proportional incidence ratio (PIR) for cutaneous malignant melanoma for non-Latino Whites by residence and origin of Social Security Number (SSN)

Residence Nativity SSN Origin	Males			Females		
	PIR/PMR	CI[a]	No.	PIR/PMR	CI[a]	No.
Los Angeles County, 1972, 82[b]						
CA/AZ						
CA/AZ	139	130-150	603	119	110-129	540
Other	100	—	28	100	—	29
Other						
CA/AZ	133	123-143	763	131	121-141	745
Other	100	—	906	100	—	683
Seattle-Puget Sound, 1974-83						
CA/AZ						
CA/AZ	111	82-151	41	126	91-169	36
Other	100	—	31	100	—	32
Other						
CA/AZ	109	85-145	50	134	105-170	61
Other	100	—	874	100	—	933

[a] CI = 95% confidence interval.
[b] Excluding Latinos/(Spanish-surnamed).

Table 4. Subgroups of cutaneous malignant melanoma: age-adjusted proportional incidence ratio (PIR) for non-Latino Whites in Los Angeles County by nativity and origin of Social Security Number (SSN)

Subgroup	Males				Females			
	Nativity		SSN origin, in migrants		Nativity		SSN origin, in migrants	
	No.	PIR	No.	PIR	No.	PIR	No.	PIR
Superficial spreading[a]								
CA/AZ	186	153[b]	170	142[b]	233	173[b]	210	129
Other	448	100	173	100	427	100	177	100
Nodular[c]								
CA/AZ	83	206[b]	76	121	64	203[b]	56	124
Other	197	100	65	100	135	100	46	100
Lentigo maligna[d]								
CA/AZ	18	154	14	161	27	209[b]	23	150[b]
Other	107	100	38	100	108	100	38	100
Ocular								
CA/AZ	19	52[b]	31	91	16	106	40	82
Other	89	100	56	100	94	100	49	100
Other noncutaneous								
CA/AZ	3	78	3	37	7	106	13	102
Other	17	100	14	100	32	100	16	100
Localized								
CA/AZ	436	157[b]	393	129[b]	503	221[b]	428	129[b]
Other	1,112	100	390	100	1,097	100	431	100
Non-localized								
CA/AZ	119	160[b]	965	131[b]	55	144[b]	293	132[b]
Other	310	100	389	100	150	100	364	100

[a] Conference interval (CI) for CA/AZ nativity: 133 - 177 (males), 152 - 196 (females); age-specific PIRs above 200 in four of 12 age groups, with CI excluding 100 in nine of 12.
[b] Confidence interval excludes 100.
[c] Confidence interval (CI) for CA/AZ nativity: 166 - 256 (males), 158 - 259 (females); age-specific PIRs above 200 in 10 of 12 age groups, with CL excluding 100 in seven of 12.
[d] Confidence interval (CI) for CA/AZ nativity: 96 - 248 (males), 141 - 309 (females); age-specific PIRs above 200 in two of 12 age groups, with CL excluding 100 in two of 12.

Table 5. Median interval since interstate inmigration to Los Angeles County and issuance of Social Security Number (SSN) by cohort

	Birth cohort						
	1890 - 99	1900 - 09	1910 - 19	1920 - 29	1930 - 39	1940 - 49	1950 - 59
Median age at risk of diagnosis	82	72	62	52	42	32	22
Approximate size of 1975 LA population in thousands[a]	20	100	250	400	500	500	400
SSN issued by year[b]	1941	1941	1941	1949	1959	1969	1979
Median year at inmigration[c]	1924	1929	1952	1953	1955	1958	1972
Median number of years from inmigration to diagnosis	53	48	25	24	22	19	5
Median number of years from SSN issuance to diagnosis	37	36	36	28	18	8	0

[a] 1980 US Census.
[b] Block G, *et al* (ref. 19).
[c] Decennial census reports (see text).

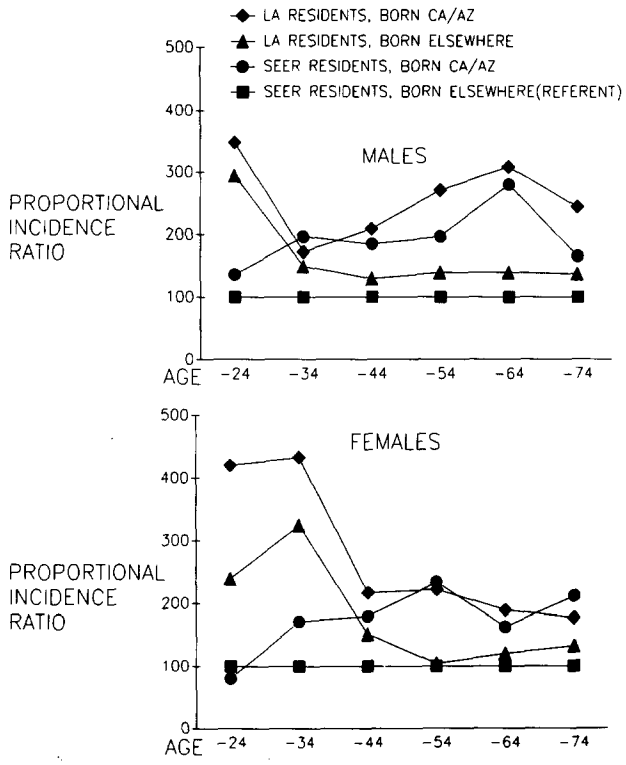

Figure 1. Proportional incidence of cutaneous malignant melanoma by age, sex, birthplace, and residence at diagnosis. Melanoma frequencies upon which PIRs are based, by 10-year age group, 15-74 are as follows. (◆) Los Angeles residence, California/Arizona born—males: 79*, 132, 139*, 158*, 138*, 58*; females: 90*, 199*, 117*, 140*, 99*, 36. (▲) Los Angeles residence, born elsewhere—males: 35*, 133, 216, 374, 500, 369; females: 35*, 178*, 223, 275, 347, 309. (●) SEER area (excepting San Franciso, Seattle) residence, California/Arizona born—Males: 7, 33*, 34*, 20, 20*, 7; females: 7, 38, 24, 23*, 10, 7. (■) SEER area residence, born other than in California/Arizona—males: 143, 386, 537, 749, 819, 655; females: 214, 531, 554, 681, 642, 501. *Results in a PIR with confidence limits excluding 100.

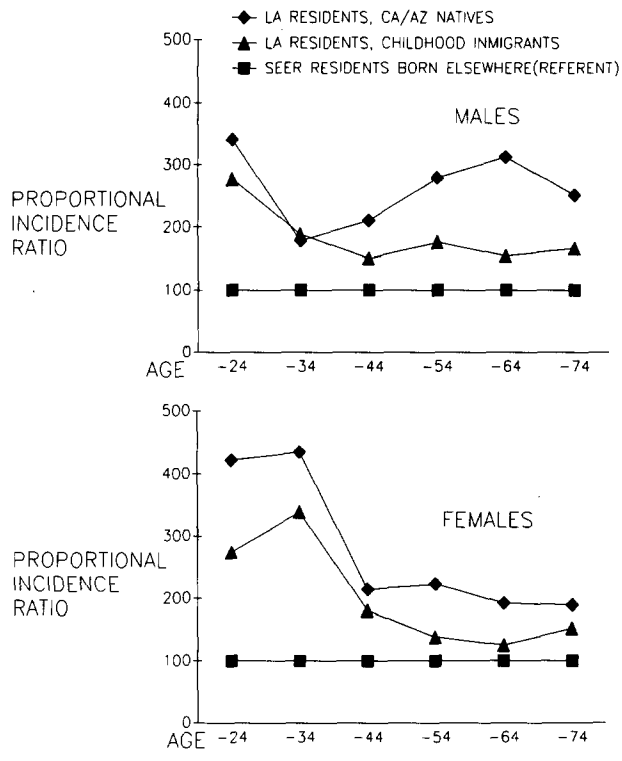

Figure 2. Effect of early exposure to high risk latitude; proportional incidence of cutaneous malignant melanoma by age and birthplace in persons resident in Los Angeles County since childhood. Melanoma frequencies upon which PIRs are based, by 10-year age group, 15-74 are as follows. (◆) Los Angeles County residence, California/Arizona born, California/Arizona SSN—males: 67, 126, 128*, 144*, 125*, 53*; females: 76, 169*, 99, 123*, 81*, 34. (▲) Los Angeles County residence, born elsewhere, California/Arizona SSN—males: 19, 84, 84, 117, 166, 195; females: 20, 91, 99, 100, 133, 182. (■) SEER area residence, born other than in California/Arizona—males: 143, 386, 537, 749, 819, 655; females: 214, 531, 554, 681, 642, 501. *When compared to analogous frequency for Los Angeles County residence, born elsewhere, California/Arizona SSN, results in a PIR with confidence limits excluding 100.

inmigrants in relation to the same referent standard. Childhood inmigrants do suffer a relatively constant adult relative risk (RR) which is about 20 percent (women) to 40 percent (men) higher than that experienced by those back home. However, there is a lifelong additional increment in the risk of natives (for males, PIR = 138; for females, PIR = 136) in comparison with the childhood inmigrants rather than the SEER as the standard; this can be attributed to the short differential period of exposure. Because this difference in absolute risk from early exposure is temporary, the RR of childhood migrants might be expected to converge upon that of natives if the effect of latitude-specific solar flux were cumulative. No such convergence was observed, even though the two groups co-resided at the same latitude for decades, generally a much longer time than they lived apart. This apparently permanent effect of childhood exposure also seems greater for NM (PIRs of 189,180) than SSM (125,157), or LMM (122,186) melanoma (except for that for LMM in men, CI for these PIRs exclude 100).

Figure 3 examines whether long-term residence in Los Angeles after adult inmigration elevates risk beyond the level that would have prevailed at home. In comparison with the stay-at-home SEER referent standard, 'adult' inmigration does seem to produce a risk elevation in the first two (men) or three (women) decades of life. However, for such young patients, entry into the work force, subsequent migration to Los Angeles, and the pertinent exposure all necessarily

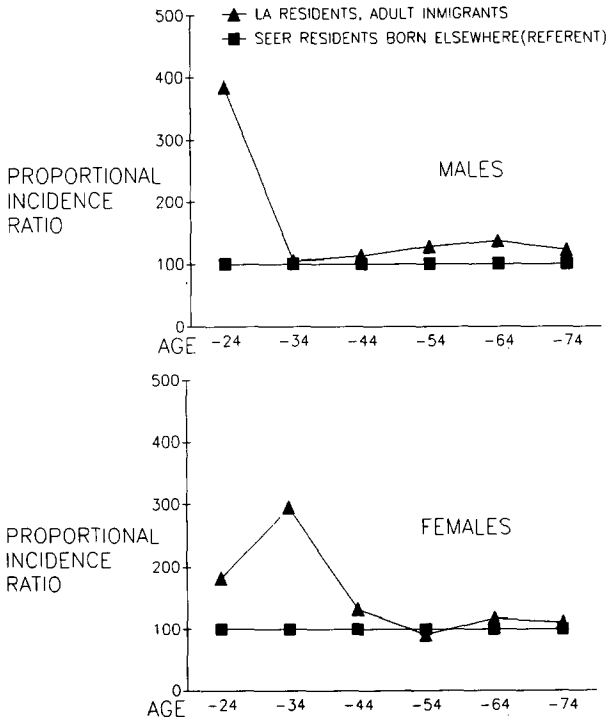

Figure 3. Effect of recent exposure to high risk latitude:proportional incidence of cutaneous malignant melanoma by age and residence at diagnosis among those not residing in California/Arizona during childhood. Melanoma frequencies upon which PIRs are based, by 10-year age group, 15-74 are as follows. (▲) Los Angeles County residence, born elsewhere, SSN issued elsewhere—males: 12*, 42, 119, 227, 274, 138; females: 5, 72*, 91, 136, 166, 101. (■) SEER area residence, born other than in California/Arizona—males: 143, 386, 537, 749, 819, 655; females: 214, 531, 554, 681, 642, 501. *Results in a PIR with confidence limits excluding 100.

took place within a short period before diagnosis. Moreover, it is likely that some who appear to have come to Los Angeles as very young adults actually are childhood inmigrants whose parents had already obtained SSNs on their behalf at the place of origin. More notable than this early increase is the absence of any increase in RR with advancing age and therefore with cumulating differential exposure, and indeed an absence of much elevated risk at all after the first decades of adult life. We assessed the possibility that known or presumed effects of ethnicity, occupation, or socioeconomic class could be responsible for all or part of this birthplace gradient. Non-Latino White cancer patients diagnosed over the period were categorized according to the ethnicity of the surname. Relative to other cancer patients in LAC, the odds of melanoma occurrence in Los Angeles are increased by roughly 10 percent for those with English, German-Dutch, Celtic, or Scandinavian surnames, and decreased by roughly 40-50 percent for those with Eastern European, or Southern European-Middle Eastern names, in each case, relative to persons having ethnically uninformative or ambiguous names. These seven groups are present in nearly identical numbers (about 40 percent English; 29 percent non-specific; 11 percent German-Dutch; eight percent Celtic; six percent Scandinavian; three percent Southern European-Middle Eastern; and two percent Eastern European) among native, early migrant, and adult migrant non-Latino Whites, and migrant status does not modify appreciably any ethnicity-specific melanoma risk. While non-Latino surname is not as sensitive as some indicators of ethnicity, it does produce a risk differential, and no migrant risk gradient at all would be predicted on the basis of surname. We then examined the effect of CA/AZ nativity within strata homogeneous for occupation and socioeconomic class. Risk for CA/AZ natives as measured by the age-standardized PIR remained comparably high within each stratum (male, female) of high (135, 130), medium (121, 130), and low (139, 120) socioeconomic class, and within each occupational stratum of professionals (157, 128), managers (146, 163), salesworkers (154, 143), clerical workers (132, 142), and craftsmen, operatives, laborers, service workers and housewives combined (154, 160).

Discussion

Alternative explanations

Coincidence is not a likely explanation for these unusual and coherent findings, nor is it likely that a simple artifact could produce such results. Some natives of a place do have exposures uncharacteristic of that place, and unrecorded changes of residence do occur between birth and work entry or work entry and diagnosis, but such misclassification is unsystematic and would not reveal or enhance the effect of childhood exposure while obscuring an effect of cumulative exposure. Since birthplace determined risk in both migrant and stay-at-home populations, the effect cannot be attributed to the determinants of migration, to differential migration of a high-risk population, or to regional habits of solar exposure. If preference for the sun, rather than origin in the sun, determined risk, the gradient would be reflected by the preferred (residential) latitude, not the latitude of birth. Emigrants from the southwestern states do not return regularly for sunshine, and northerners living in the southwest do not protect themselves preferentially from the sun. The only non-solar predictor of melanoma risk linked to latitude is skin color; the prevalence of Latinos in the southwest would simulate protection, not endangerment, and other ethnic differences do not seem import-

ant. The effect is evident within each social class and occupational category, and for each anatomic site, stage, and form of cutaneous melanoma, but not for noncutaneous melanoma. This link between early susceptibility and lifelong risk is completely consistent with the reported birth-cohort effect in melanoma risk;[27] a childhood experience, like an addicting habit, can permanently characterize a generation.

Consistency with other findings and interpretation

Age at migration from Europe to Australia[28] and New Zealand[29] (across about 20 degrees of latitude) has been linked to melanoma mortality, and incidence.[30] In the largest of these studies,[30] age at migration was responsible for the effect, independent of constitutional determinants of melanoma and of stated patterns of sun exposure. Because of the number of migrant subjects, however, it could not be separated from the subsequent duration of adult residence. Migration and melanoma risk have also been studied in Israel[31] with similar results, although age at immigration was not examined independently; duration of residence in Israel was held to be the critical factor. Recently, the melanomas occurring in a cohort of American nurses were found to be more common after teenage residence at a lower latitude.[32]

In Australia,[30] as here, a sharp early elevation in melanoma rate rapidly followed upon youthful migration. We found this rapid elevation more pronounced in women, whether for behavioral or physiological reasons.

Some[33] have hypothesized that LMM might have a different etiology than other types of melanoma, not especially linked to early solar exposure. We found the link of LMM with nativity and, at least in women, with early migration, to be no less strong than for other melanomas. We did find an especially strong link between NM and differential exposure during the first two decades of life, coupled with a rather weak link for exposure after that time. Consistent with others,[34] we found no evidence that nativity or early migration increased the occurrence of noncutaneous melanoma.

Experimental photobiology and the classical animal studies of skin carcinogenesis lead us to expect a short latency between solar exposure and effect. The direct action of solar UVB upon the base structure of DNA or transient chemical intermediaries[35] cannot explain such a strong association with an exposure so remote in time. While an age-specific solar influence upon local or systemic physiologic protective mechanisms (immunologic[36] or hormonal[37]) cannot be ruled out, a more appealing clue to the mechanism is the solar induction of benign melanocytic nevi,[38] which by size and number are consistently strong predictors of melanoma.[39] While not all cutaneous melanomas occur in the presence of a nevus, or on skin with multiple or large nevi, and while there is only indirect evidence suggesting that benign nevi act as or are linked to more plausible precursors,[40] it does seem reasonable that the number and size of nevi induced during childhood might serve as an indication of the number of cells at risk of becoming malignant and at least partly underlie the observed link with childhood exposure.

More troublesome is the inconsistency between our observations and the proposition that cumulative or periodic adult exposure to a sunny latitude is linked to melanoma incidence, even though a link has been presumed on grounds of experimental evidence, and would provide a logical bridge between the prevalence of nevi and the appearance of malignant melanocytes. Diverse epidemiologic findings have been offered in support of such a relationship,[41] but, overall, the evidence is not conclusive. Some evidence of causation in adulthood is ambiguous, difficult to replicate, or of questionable generalizability; this includes trends in the seasonality of diagnosis,[42] acquired immunosusceptibility,[43] and exposure to artificial sources of UV radiation[44] and occupational chemicals.[45,46] Attempts to incriminate occupational or other measures of cumulative habitual exposure have produced negative as well as positive associations with melanoma.[41,47,48] While the associations with periodic recreational exposure have generally been more consistently positive, bias in questioning is difficult to avoid, and the magnitude of the risks has been no larger than that found in this descriptive study. Stronger support is thought to come from the demonstration of links between melanoma risk and other photobiologic outcomes,[41] including past sunburn,[49,50] past nonmelanoma skin cancer,[51] and actinic skin damage,[33] but measurement of skin color and a quantitative assessment of the role it plays in determining actinic damage is difficult.[52] Moreover, the statistical emphasis on lifetime experience has meant that the role of childhood solar exposure has been inadequately evaluated as a confounder in all assessments. This is unfortunate because sun-seeking behavior in adulthood is likely to have been learned in childhood. Direct attempts to specify the age/time frame of specific exposures are few as yet and have not produced coherent results.[32,41,53-55] It is possible that adult exposure may not play the important role that we have assumed previously.

Implications

A major emphasis in the control of melanoma has long been placed on the reduction of solar exposure among adults. Such efforts may not be cost-effective and, if tanning provides some protection, which seems pos-

sible on both physiologic[56] and epidemiologic[57] grounds, risk may sometimes even be increased. Increasing recognition of the importance of early exposure should encourage parental programs to limit the solar exposure of children.[58] Whether or not programs based on this strategy are ever proved effective, it is important to determine precisely the age at risk, because a different strategy will be required for older children and teenagers.[59] Perhaps more emphasis should be placed on the early education of constitutionally high-risk individuals to encourage lifelong regular self-examination. Unlike most cancers, melanoma is linked to high educational status,[12] and a good educational program may prove unexpectedly effective.

Those concerned about the impact of stratospheric ozone depletion[60] point to the current increase in melanoma incidence[61] as evidence of a major negative outcome.[62] If solar radiation does act mostly in childhood, the cited increases, largely reflecting diagnoses in older people, indicate the status of the ozone shield a generation or more ago, and the real impact of recent ozone depletion will not be evident for decades.

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