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Increasing Incidence of Lentigo Maligna Melanoma Subtypes: Northern California and National Trends 1990–2000

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Worldwide, lentigo maligna melanoma (LMM) comprises 4%–15% of cutaneous melanoma and occurs less commonly than superficial spreading or nodular subtypes. We assessed the incidence of melanoma subtypes in regional and national Surveillance, Epidemiology, and End Results (SEER) cancer registry data from 1990 to 2000. Because 30%–50% of SEER data were not classified by histogenetic type, we compared the observed SEER trends with an age-matched population of 1024 cases from Stanford University Medical Center (SUMC) (1995–2000). SEER data revealed lentigo maligna (LM) as the most prevalent *in situ* subtype (79%–83%), and that LMM has been increasing at a higher rate compared with other subtypes and to all invasive melanoma combined for patients aged 45–64 and ⩾65 y. The SUMC data demonstrated LM and LMM as the only subtypes increasing in incidence over the study period. In both groups, LM comprised ⩾75% of *in situ* melanoma and LMM ⩾27% of invasive melanoma in men 65 y and older. Regional and national SEER data suggest an increasing incidence of LM and LMM, particularly in men ⩾age 65. An increased incidence of LM subtypes should direct melanoma screening to heavily sun-exposed sites, where these subtypes predominate.

Key words: epidemiology/histopathology/incidence/melanoma
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Separation of cutaneous melanoma into distinct "histogenetic" subtypes was first proposed by Clark *et al* in the 1960s, and resulted in the classification of melanoma into four main subtypes: superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna (LM) melanoma (LMM), and acral lentiginous melanoma (ALM) (Clark *et al*, 1969; Arrington *et al*, 1977; Coleman *et al*, 1980). Worldwide, the superficial spreading subtype predominates, followed by nodular, LM, and acral lentiginous subtypes (Elwood *et al*, 1987; English *et al*, 1987; Castel *et al*, 1990; Vazquez-Botet *et al*, 1990; Carmichael *et al*, 1992; Jelfs *et al*, 1994; Oumeish, 1997; Jones *et al*, 1999). Exceptions, however, have occurred in Asian countries where most cases were of the acral lentiginous subtype (Kuno *et al*, 1996; Chen *et al*, 1999; Ishihara *et al*, 2001), and in some reported series of head and neck cases, in which LM and LMM have shown a higher incidence, but remained less common than superficial spreading and nodular growth patterns (Ringbord *et al*, 1993; Cox *et al*, 1996).

Abbreviations: ALM, acral lentiginous melanoma; APC, annual percentage change; LM, lentigo maligna; LMM, lentigo maligna melanoma; MM, millimeters; NCI, National Cancer Institute; NM, nodular melanoma; SEER, Surveillance, Epidemiology, and End Results; SSM, superficial spreading melanoma; SUMC, Stanford University Medical Center; UV, ultraviolet

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Prior studies have shown an increased age-specific incidence of both LM and LMM (Little *et al*, 1980; Newell *et al*, 1988; Jones *et al*, 1999), although the LM subtype (whether *in situ* or invasive) is still recognized as comprising only a small percentage of cutaneous melanoma (Little *et al*, 1980; Langley *et al*, 1998). Based on analysis of the Swedish Cancer Registry from 1961 to 1998 (Hemminki *et al*, 2003), LM was reported as the most common *in situ* histogenetic type, occurring almost three times more frequently than SSM. In a regional analysis of incidence trends from 1976 to 1994 in the Stockholm–Gotland area (Månsson-Brame *et al*, 2002), however, SSM far outnumbered LMM for invasive cases, although LMM incidence increased significantly in both men and women. Recent characterization of the United States Surveillance, Epidemiology, and End Results (SEER) cancer registry of the National Cancer Institute (NCI) for incidence of *in situ* and invasive melanoma subtypes has not been reported. Furthermore, confirmation of trends reported in the regional/national SEER data has not been undertaken at the local level where complete and precise reporting of melanoma subtype may be more feasible (Hall *et al*, 2003).

We assessed melanoma subtype incidence according to the four main histogenetic types in national and northern California SEER data from 1990 to 2000, and compared it with an age-matched population at Stanford University Medical Center (SUMC). We believe that LM/LMM subtypes account for a larger proportion of *in situ* and invasive melanoma than reported previously.

Results

SEER data analysis Analysis of the SEER melanoma incidence data for subtyped tumors diagnosed from 1990 through 2000 revealed significant, previously unreported trends for both LM and LMM. Over this 10-y period, LM comprised 83% of all subtyped *in situ* melanoma, and LMM accounted for 12% of all subtyped invasive melanoma in the northern California region. Nationwide results were similar, with LM comprising 79% and LMM 12% of subtyped tumors (Table I). Notably, the incidence of the LM/LMM subtypes increased nearly every year during this time period: 73% of all subtyped *in situ* melanomas were classified as LM in 1990 compared with 81% in 2000. Similarly, 8.4% of all subtyped invasive melanomas were classified as LMM in 1990 compared with 14% in 2000. These trends were most prominent in older males. For men aged 65 y or greater, the incidence of LMM increased from 20% in 1990 to 27% in 2000, when compared with all subtyped invasive tumors.

In both men and women aged 45–64, diagnosis of LM (compared with all melanoma) increased by 52% between 1990 and 2000 (actual rate increase 3.8–5.8 per 100,000), with an increase of 96% for individuals $\geqslant$65 y at the time of diagnosis (actual increase 12.1–23.7 per 100,000) (Table II). Both these trends were significant at p-values of less than 0.05, with annual percentage changes (APC) of 3.9 and 6.8, respectively (Table II). In comparison, SSM *in situ* showed a smaller, but significantly increased APC (3.7) only in the 65 y and older age group.

During this time period, the incidence of LMM also increased significantly. LMM incidence increased by 88% (0.8–1.5 per 100,000) in the 45–64 y old age group (APC 6.0, $p<0.05$) and by 105% (3.9–8.0 per 100,000) in the $\geqslant$65 y old group (APC 5.5, $p<0.05$). In comparison, the incidence of all invasive melanoma during this time period increased by only 21% (24.5–29.7 per 100,000) for the 45–64 y age group (APC 2.3, $p>0.05$) and by 53% (38–58 per 100,000) for the $\geq$ 65 y age group (APC 4.2, $p<0.05$). Incidence trends for invasive SSM, NM, and ALM over the decade are listed in Table II. Significant, but smaller increases in APC values were noted only for SSM (3.7) and NM (2.8) in the 65 y and older age group. As the trends were independently significant using the same incidence data and standardization, the higher APC for LMM represented a true difference between the subtypes over the time period.

SUMC data analysis The SUMC population consisted of 1024 primary cutaneous melanomas classified into the four main histogenetic subtypes (Table III). Forty-eight additional melanoma variants were identified including 18 desmoplastic, 19 spindle cell type, three minimal deviation, three nevoid, four Spitzoid, and one small cell variant. In addition, 34 *in situ* and 48 invasive tumors (8% of total cases) could not be subtyped. Fifty-two percent (220 of 420) of *in situ* cases were LM, and 11% (67 of 604) of invasive melanomas were LMM, which represented a greater proportion than NM (5%). The median age at diagnosis in the SUMC population was 54 (range 17–99), with LM and LMM occurring mainly in older patients (median ages 69 and 71, respectively), and on heavily sun-exposed sites (85% of LM and 77% of LMM). The proportion of LM compared with all subtyped cases increased from 41% in 1995 to 61% in 2000, and LMM increased from 10% to 16% over the same period. All other subtypes (*in situ* and invasive) decreased over the same time period.

Comparison of regional and national data Melanoma subtype data from SUMC were compared with the NCI SEER cancer registry for comparable years of diagnosis and age range (Table IV). Males comprised 56% of patients in the SEER data and 57% of SUMC cases, and gender similarities were maintained when the SEER data was examined according to region, comparing the San Francisco–Oakland, CA registry with the other national registry sites. The SEER patient population was predominantly diagnosed with invasive tumors (63% in California and 69% in non-California sites), as was 58% of the SUMC population. The anatomic site of melanoma was also consistent between the California and non-California SEER sites and the SUMC data, with SEER data revealing 68% of LM and 64% of LMM located on the head or neck.

Our analysis of melanoma subtypes in the SEER data revealed that the LM/LMM subtypes were diagnosed at a higher incidence than previously reported, and that this increase was most notable in the older male segment of the population. Although the size of the patient population in our regional data from SUMC was too small to perform trend analysis, we were able to observe the incidence of LM/LMM subtypes over the entire time period and in specific subgroups.

The proportion of LM in men aged 65 y or older, compared with all subtyped *in situ* melanomas, was 91% in the SEER data and 75% in the SUMC data (Table IV). Similarly, LMM occurred in 27% of men in this age group in the SEER data and 30% in the SUMC data, when compared with all subtyped invasive melanomas. Among subtyped *in situ* melanoma in men aged 45–64 y, LM comprised 79% and 49% in the SEER and SUMC data, respectively, and of subtyped invasive tumors, LMM accounted for 11% and 10% (SEER and SUMC, respectively).

Discussion

In the late 1960s, Clark *et al* initially proposed three main variants of melanoma (SSM, LMM, and NM), which were believed to demonstrate distinct clinical, histopathological, and biological features (Clark *et al*, 1969). ALM was added as a fourth major clinicopathologic type in the 1970s (Arrington *et al*, 1977; Coleman *et al*, 1980). Molecular analysis has demonstrated different patterns of cell death, oncogene expression (Miracco *et al*, 1998), gene amplification (Bastian *et al*, 2000), and *BRAF* mutation frequency (Sasaki *et al*, 2004) among the four main subtypes. But, the practice of subtyping cutaneous melanoma has been criticized over whether distinction among subtypes is based on anatomic site alone, or whether melanoma subtype affects overall prognosis (Ackerman, 1980, 2000; Ackerman and David, 1986). Likewise, the lack of uniformly agreed upon histologic criteria for classification of the four major types has resulted in moderate to significant interobserver variability in

Table I. National Cancer Institute SEER program registry data regarding melanoma subtype incidence by region, 1990–2000, patient age range 20–99 y

	San Francisco–Oakland	Non-California[a]	Combined data including NOS/other cases[b]
In situ subtypes			
Lentigo maligna *in situ* (%)	1598 (83)[c]	7436 (79)[c]	9034 (43)
Superficial spreading melanoma	304 (16)	1937 (20)	2241 (11)
Nodular melanoma	0 (0)	4 (0.04)	4 (0.02)
Acral lentiginous melanoma	17 (1)	90 (1)	107 (5)
Total *in situ* tumors	1919 (37)[d]	9467 (31)[d]	11386 (54)
Invasive subtypes			
Lentigo maligna melanoma[c]	393 (12)[c]	2634 (12)[c]	3027 (7)
Superficial spreading melanoma	2308 (72)	15367 (72)	17675 (39)
Nodular melanoma	435 (14)	2883 (14)	3318 (8)
Acral lentiginous melanoma	72 (2)	393 (2)	465 (1)
Total invasive tumors	3208 (63)[d]	21277 (69)[d]	24485 (55)

[a]Non-California regions include Hawaii; Utah; Connecticut; Detroit, Michigan; Iowa; New Mexico; Seattle-Puget Sound, Washington; and Atlanta, Georgia.
[b]Percentage calculated as total subtyped *in situ* or invasive tumors divided by total *in situ* or invasive tumors, including subtyped, unsubtyped (NOS), and subtypes not included in the four major categories (Other). Other subtypes (desmoplastic, spindle cell, amelanotic, Spitzoid, etc.) accounted for $<5\%$ of the total cases.
[c]Number displayed represents the total subtyped cases within study group as described in Material and Methods. Percentage calculated as individual subtype divided by total subtyped cases of *in situ* or invasive melanoma and displayed in parentheses.
[d]Percentage calculated as total subtyped *in situ* or invasive tumors per northern California or non-California SEER regions divided by total subtyped cases per region(s) and displayed in parentheses.
SEER, Surveillance, Epidemiology, and End Results; NOS, not otherwise specified.

subtyping in some studies (Heenan *et al*, 1984; Krieger *et al*, 1994; Corona *et al*, 1996).

Worldwide melanoma data have also shown conflicting results in terms of the impact of subtype on prognosis, and most multivariate analyses have shown that histogenetic type is not an independent prognostic variable for survival after controlling for tumor thickness (Ringbord *et al*, 1993; Cox *et al*, 1996; Kuno *et al*, 1996). Major exceptions have, however, arisen in the settings of ALM and LMM (Urist *et al*, 1984; O'Brien *et al*, 1991; Kuchelmeister *et al*, 2000).

LMM differs markedly from SSM and NM in that it has no nevus precursor, is linked to cumulative, rather than intermittent sun exposure, occurs in older individuals, and has a significantly longer period of intraepidermal growth compared with SSM (Clark and Mihm, 1969; Clark *et al*, 1975; McGovern *et al*, 1980; Sagebiel, 1996). Long-term ultraviolet (UV) radiation exposure is believed to be the most important risk factor for the development of LM/LMM (Holman *et al*, 1983; Holman and Armstrong, 1984; Elwood *et al*, 1987). In some series, LMM has been associated with improved prognosis compared with SSM and NM (Urist *et al*, 1984; O'Brien *et al*, 1991), whereas other studies have shown no significant difference in disease-free or overall survival compared with other histologic subtypes, when matched for tumor thickness (Koh *et al*, 1984; Langford *et al*, 1993; Cox *et al*, 1996).

Further controversy has arisen in the setting of the LM subtype itself. Whereas some authors have considered LM as only a precursor to melanoma (Clark and Mihm, 1969; Barnhill and Mihm, 1993), whereas, others have classified LM as a true melanoma *in situ* (Dubow and Ackerman, 1990; Cohen, 1995). Two distinct categories have been proposed based on this division: (1) the term "LM" for the melanoma precursor in the setting of atypical melanocytic hyperplasia alone and (2) the term "melanoma *in situ*, LM type" representing the true *in situ* melanoma defined by melanocytic hyperplasia, pagetoid spread, confluence of melanocytes replacing the basilar region, uniformity of cytological atypia, and nesting of uniformly atypical melanocytes (Flotte and Mihm, 1999; Tannous *et al*, 2000). Slow progression from the precursor lesion to obvious melanoma *in situ* may explain this dichotomy. We were careful to include only cases definitively diagnosed as melanoma *in situ*, LM type and to exclude cases of junctional atypical melanocytic hyperplasia, even when "early LM" was suggested by the dermatopathologist.

Most of the worldwide melanoma subtype incidence data do not distinguish between *in situ* and invasive cutaneous melanoma. Globally, LM/LMM is estimated to account for 4%–15% of all melanomas, and 10%–26% of all head and neck melanomas (McGovern, 1970; Donnellan *et al*, 1972; Little *et al*, 1980; McGovern *et al*, 1980; Popescu *et al*, 1985; Langford *et al*, 1993; Ringbord *et al*, 1993). In their study of invasive melanoma incidence in New Zealand, Jones *et al* (1999) reported increased age-specific rates for LMM and NM, most notably after age 70 y, with SSM showing decreased incidence after this age. In this analysis, though, SSM far outnumbered NM and LMM cases overall, with an age-specific annual rate of 36.3 of 100,000 compared with 2.8 of 100,000 for NM and 2.4 of 100,000 for LMM. In the US, the best evidence for an increased incidence of LM is based on unpublished 1995 data from a large private

Table II. National Cancer Institute SEER program registry data, rate of melanoma incidence, 1990–2000, patient age range 20–99 y

	Age group	Actual rate change[a]	APC[b]	Confidence interval of APC
Lentigo maligna				
In situ	20–44	0.4–0.5	2.0	−0.6–4.6
	45–64	3.8–5.8	3.9[c]	1.7–6.2
	⩾65	12.1–23.7	6.8[c]	5–8.7
Invasive	20–44	0.1–0.1	−0.4	−5.7–5.2
	45–64	0.8–1.5	6.0[c]	2.7–9.3
	⩾65	3.9–8.0	5.5[c]	3.4–7.5
All melanoma				
In situ	20–44	2.9–5.1	6.6[c]	5.3–7.9
	45–64	8.3–18.7	8.7[c]	7.3–10.1
	⩾65	17.4–43.9	9.8[c]	8.8–10.8
Invasive	20–44	11.7–11.8	0.5	−0.4–1.5
	45–64	24.5–29.7	2.3[c]	1.3–3.2
	⩾65	38–58	4.2[c]	3.4–5.0
SSM (invasive)	20–44	6.0–5.7	−0.6	−1.5–0.3
	45–64	11.3–12	0.7	−0.6–2.0
	⩾65	11.2–17	3.7[c]	2.4–5.2
NM (invasive)	20–44	1.0–0.6	−4.2[c]	−6.2 to −2.3
	45–64	1.8–1.8	−0.2	−2.9–2.6
	⩾65	4.4–4.7	2.8[c]	0.3–5.3
ALM (invasive)	20–44	0.0–0.1	8	−3.8–21.3
	45–64	0.2–0.2	3.1	−3.2–9.7
	⩾65	1.1–0.8	−0.1	−5.9–4.2

[a]Actual change of incidence rate per 100,000 persons.
[b]The annual percentage change was calculated by fitting a least squares regression line to the natural logarithm of the rates.
[c]Trend is statistically significant with a p-value < 0.05.
SEER, Surveillance, Epidemiology, and End Results; APC, annual percentage change; SSM, superficial spreading melanoma; NM, nodular melanoma; ALM, acral lentiginous melanoma.

dermatopathology laboratory in which 54% of *in situ* melanomas were reported to be of the LM subtype (Cohen, 1999).

To our knowledge, there has been no recent characterization of SEER data regarding incidence of invasive and *in situ* melanoma according to histogenetic subtype. Newell *et al* (1988) reported histological subtype incidence rates for SSM, NM, and LMM based on 1973–1981 SEER data and according to four anatomic sites (face, trunk, arm/shoulder, and leg/hip). Not surprisingly, analysis of over 1300 cutaneous melanomas revealed that age-specific incidence for melanoma of the face steadily increased with age, with LMM rates being higher in SEER geographic locations with higher UV indices and SSM rates being higher in areas with lower UV indices. When all anatomic and geographic locations were combined, however, SSM remained the subtype with the highest incidence, although the incidence of LMM and NM was similar in both males and females.

Furthermore, this publication highlighted the potential bias in interpreting subtype incidence because of the large proportion of melanoma not classified according to histologic subtype in the SEER registry, which accounted for $>52\%$ of cases analyzed in both men and women. But, no differences were apparent when age-specific incidence curves for the unclassified melanoma cases were compared with those of the classified melanomas according to anatomic site. The authors concluded that the similarity of the curves provided reassurance that patients with classifiable melanoma were likely representative of the non-classifiable cases, at least for the major variables of age and gender.

Incomplete subtype data are an unavoidable limitation of the SEER registry, and as with other reports of melanoma subtypes (Newell *et al*, 1988; Carmichael *et al*, 1992; Ringborg *et al*, 1993), we can only draw conclusions from the subtyped cases. There are clearly a small percentage of melanomas in any dermatopathology practice that cannot be accurately classified into a specific histogenetic type. This factor certainly contributes to the large percentage of unclassified melanomas in the SEER data (30%–50% per y) along with other probable factors, e.g., non-dermatopathologist interpretation of cutaneous melanoma, lack of belief in the concept of melanoma subtyping, or failure to report the subtype data at the local registry level. The advantage of using our hospital-based analysis to confirm the trends in the SEER data lies in greater precision in reporting of histologic subtype (only 8% SUMC melanoma unclassified) as well as more complete reporting of both *in situ* and invasive melanoma.

Hospital-based reporting to the SEER registries has generally shown a high case ascertainment rate ($>97\%$), although this rate may be much lower for melanoma (Koh *et al*, 1992; Zippin *et al*, 1995; Merlino *et al*, 1997). Underreporting of melanoma may be related to treatment administered in outpatient, non-hospital settings, particularly for early-stage, localized disease (Koh *et al*, 1992). The most accurate calculation of national incidence rates of melanoma would combine SEER data and information from additional state cancer registries. Recent analysis comparing melanoma incidence rates between SEER registries and National Program of Cancer Registries (NPCR) has suggested increased case ascertainment and reporting in the NPCR registries, which provide information for cancer control at the local level (Hall *et al*, 2003). Likewise, calculation of SEER incidence rates tends to include only invasive melanoma (Hall *et al*, 1999) without specific attention to trends in the more common *in situ* cases.

Underreporting of cutaneous melanoma to the SEER registry in northern California was reported to increase from 4% in 1973 to 16% in 1985 (Seiffert, 1992) with larger numbers of *in situ* cases missed, as they were more likely to be diagnosed and treated solely in private physicians' offices. This issue is particularly relevant given the prevalence and availability of Mohs surgery in northern California for treatment of LM, where similarly, these melanomas *in situ* may not be evaluated by a hospital-based pathology service, and thus may not reported to the regional SEER registry.

The increased incidence of LM and LMM in the regional and national SEER data from 1990 through 2000 was confirmed in the hospital-based SUMC analysis. But, there

Table III. Stanford University Medical Center melanoma subtype data, 1995–2000

In situ subtypes	Lentigo maligna *(in situ)*	Superficial spreading melanoma *in situ*	Acral lentiginous melanoma *in situ*
Number (%)[a]	220 (52)	196 (47)	4 (1)
Median age (range)	69 (25–94)	51 (24–99)	67 (39–78)
Predominant site (%)	Head/Neck (69)	Trunk (48)	Foot (100)
Gender			
Male	140	95	2
Female	80	101	2

Invasive subtypes	Lentigo maligna melanoma	Superficial spreading melanoma	Nodular melanoma	Acral lentiginous melanoma
Number (%)[a]	67 (11)	490 (81)	29 (5)	18 (3)
Median age (range)	71 (36–96)	48 (17–96)	58 (25–81)	63 (19–84)
Median breslow depth (range)[b]	0.52 (0.16–5.0)	0.55 (0.1–10)	3.0 (1.0–16)	2.0 (0.3–9.0)
Predominant site (%)	Head/Neck (66)	Trunk (50)	Trunk (35)	Foot (72)
Gender				
Male	48	273	18	9
Female	19	217	11	9

[a]Percentage calculated as individual subtype divided by the total cases of *in situ* or invasive melanoma. Median age and range are displayed in y.
[b]Breslow depth is displayed in millimeters (mm).

were slightly more invasive tumors diagnosed in the SEER population compared with SUMC. This may be related to improved health care access or closer follow-up within the SUMC population compared with sites participating in the SEER registry, but is more likely because of underreporting of *in situ* tumors in the SEER database. Despite the smaller number of SUMC cases, the Stanford data accurately reflect current US melanoma incidence trends (Geller *et al*, 2002), and both datasets revealed notably similar LM/LMM incidence in the cohort of middle-aged and older men.

Table IV. General characteristics and proportion of LM and LMM subtypes in the SEER and SUMC patient populations

	SEER	SUMC
Median age, all cases (range)	60 (20–99)	54 (17–99)
Percentage in each age group (number) (y)		
20–44	23 (8326)	29 (292)
45–64	35 (12465)	37 (376)
$\geqslant$65	42 (15080)	34 (347)
Percentage male (number)	56 (20054)	57 (585)
Percentage female (number)	44 (15817)	43 (439)
Proportion of LM in males[a] (y, %)		
45–64	79	49
$\geqslant$65	91	75
Proportion of LMM in males (y, %)		
45–64	11	10
$\geqslant$65	27	30

[a]The number of tumors identified as LM or LMM was divided by the total number of *in situ* or invasive subtyped tumors within the specified age group and expressed as a percentage.
SEER, Surveillance, Epidemiology, and End Results; LM, lentigo maligna; LMM, lentigo maligna melanoma; SUMC, Stanford University Medical Center.

Analysis of the trends of melanoma incidence in the SEER data revealed that age-adjusted rates of both LM and LMM significantly increased from 1990 to 2000 in people aged 45–64 y and those 65 y and older. For both age groups, the LMM incidence rate demonstrated a higher annual percent change than individual SSM, NM, and ALM subtypes and in comparison with all invasive melanoma combined. The reported dramatic rise in melanoma incidence over the past three decades does not appear to be simply a result of increased surveillance and early detection of thin tumors, but seems to represent a true increase in melanoma rates, in part because of changes in lifestyle that have led to increased UV exposure (Armstrong, 1988; Burton and Armstrong, 1988; Rigel, 1997; Dennis, 1999). This is especially relevant for the LM and LMM subtypes that typically arise on chronically sun-damaged skin. A true increase in the proportion of LMM compared with all invasive melanomas, however, may have a favorable effect on melanoma mortality rates as LMM tends to be thinner at the time of diagnosis than other histogenetic patterns (nodular and desmoplastic) and may be associated with reduced risk of metastasis compared with other subtypes (Urist *et al*, 1984; O'Brien *et al*, 1991).

Although opinions vary as to whether subtyping melanoma into distinct morphologic growth patterns is valid (Weyers *et al*, 1999) or has prognostic import, there is no question that early detection of thinner melanomas leads to improved prognosis (Clark *et al*, 1989; Balch *et al*, 2001). Our northern California hospital-based data show increased incidence for both LM and LMM over the study period and

correlate with the 1990–2000 SEER data. Health care providers should be alerted to the need for routine examination of chronically sun-exposed skin in older, fair-complexioned individuals for detection of LM, now the most common *in situ* melanoma subtype in middle-aged and older men in the US, and for its invasive counterpart, LMM. As a progressively larger proportion of the US population ages, the incidence of these melanoma subtypes may continue to rise. Ultimately, LM and LMM must receive greater public and health care attention.

Materials and Methods

Permission was granted by the Surveillance Research Program of the NCI to obtain incident cases of melanoma from the SEER Database (www.seer.cancer.gov) (SEER*Stat database, 2003). Data were obtained from the nine regions included in the SEER database, including: San Francisco–Oakland, California; Hawaii; Utah; Connecticut; Detroit, Michigan; Iowa; New Mexico; Seattle-Puget Sound, Washington; and Atlanta, Georgia. Stanford reported registry information to the Northern California Cancer Center, which is responsible for the Greater Bay Area Cancer Registry and provides information to the NCI SEER program. Registry information from Stanford was incorporated into the San Francisco–Oakland region in the SEER database.

SEER data were compiled for those patients diagnosed from 1990 through 2000, and from ages 20 to 99 y. Individuals of all races and both genders were included with *in situ* or invasive melanoma of the skin [International Classification of Diseases for Oncology (ICD-O) morphology codes 8721 (NM), 8742 (LMM), 8743 (SSM), and 8744 (ALM), and topography codes C44.0 through C44.9]. For comparison with SUMC data, cases with widely metastatic disease on presentation and those with non-cutaneous primary tumors (i.e., ocular, mucosal) were excluded, as were unclassified cases of "melanoma, histology not otherwise specified" (NOS). A total of 35,871 cases fulfilled the inclusion criteria.

SEER registry data demonstrated that 30%–50% of total melanoma cases (*in situ* or invasive) were not subtyped (NOS) for any given year between 1990 and 2000. Similar large proportions of unclassified melanoma were present in the SEER data from 1980 to 2000, making the earlier comparison less useful. SEER analysis from 1973 to 1981 (Newell, *et al*, 1988), however, revealed similar age- and gender-specific incidence data between subclassified and unclassified cases according to anatomic site, suggesting that histologic subtype of the classified cases may be representative of the unclassified cases. Exclusion of unclassified cases in the SEER dataset was made on this basis for the SUMC data comparison.

SEER data were compared with SUMC data according to age, anatomic site, subtype incidence, and proportion of *in situ* and invasive tumors. To explore geographical effects, we re-examined these parameters within the SEER geographic subset of San Francisco–Oakland, CA site *versus* the remaining geographic locations. Breslow thickness of invasive tumors was difficult to compare directly because the coding system of the SEER data allowed coding of depth only up to 9.9 mm, and many tumors in our dataset exceeded this depth. LM/LMM incidence was directly compared in a cohort of middle-aged and elderly males in the two study populations.

Incidence trends were analyzed for *in situ* and invasive melanomas diagnosed between 1990 and 2000, using the SEER*Stat software (Surveillance Research Program, NCI) version 5.0.17 (www.seer.cancer.gov/seerstat). Rates were age adjusted and standardized to the 2000 US population. Data were analyzed separately for three age groups (20–44, 45–64, and $\geqslant$65 y). The APC was calculated by fitting a least squares regression line to the natural logarithm of the rates. Selection criteria were the same as above, with the exception that "all melanomas" were selected for comparison with LM/LMM and other subtypes using the ICD-O codes 8720–8790, which included tumors designated "Melanoma, NOS" in addition to those specified as a particular subtype.

Following Human Subjects approval at SUMC, a retrospective review of the Stanford Department of Pathology dermatopathology database was conducted from January 1995 through June 2000. Archived SUMC data regarding melanoma subtype and individual histology slides were not accessible before January 1995. Information regarding melanoma subtype (SSM, NM, LMM, ALM) for both *in situ* and invasive cutaneous melanomas was obtained along with Breslow depth, patient age at the time of diagnosis, melanoma location, and gender. Chronically sun-exposed anatomic sites were defined as the head, neck, arms, and shoulders.

Histopathological diagnosis of melanoma subtype was made by one of three dermatopathologists at SUMC over the 5-y period using established histologic criteria (Elder and Murphy, 1991). Cases of mucosal melanoma and other rare melanoma variants, i.e., malignant blue nevus, melanoma arising from large congenital nevi, melanoma of the soft parts, and metastatic melanoma, were excluded as were cases in which primary cutaneous melanoma was diagnosed synchronously with widespread metastasis. The number of desmoplastic, spindle cell, Spitzoid, minimal deviation, and nevoid melanoma cases was noted at each institution, but not further analyzed.

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