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Acral Lentiginous Melanoma: Incidence and Survival Patterns in the United States, 1986-2005

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Abstract

Objective—To examine incidence and survival patterns of acral lentiginous melanoma (ALM) in the United States.

Design—Population-based registry study.

Setting—We used the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute to evaluate data from 17 population-based cancer registries from 1986 to 2005.

Participants—1413 histologically confirmed cases of ALM were reported.

Main Outcome Measure—Incidence and survival patterns of patients with ALM.

Results—The age-adjusted incidence rate of ALM overall was 1.8 per million person-years. The proportion of ALM among all melanoma subtypes was greatest in Blacks (36%). ALM had five- and ten-year melanoma-specific survival rates of 80.3% and 67.5%, respectively, which were less than for all cutaneous malignant melanoma (CMM) overall 91.3% and 87.5%, ($p < 0.001$). ALM five- and ten-year melanoma-specific survival rates were highest in Non-Hispanic Whites (82.6% and 69.4%), intermediate in Blacks (77.2% and 71.5%), and lowest in Hispanic Whites (72.8% and 57.3%) and Asian/Pacific Islanders (70.2% and 54.1%). ALM thickness and stage correlated with survival in gender and the different racial groups.

Conclusions—Population-based data showed that ALM is a rare melanoma subtype, although its proportion amongst all melanoma is higher in people of color. ALM is associated with a worse prognosis than CMM overall. Hispanic Whites and Asian/Pacific Islanders have worse survival rates than other groups, and factors such as increased tumor thickness and more advanced stage at presentation are the most likely explanations.

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Introduction

Cutaneous malignant melanoma (CMM) is the most lethal form of skin cancer and accounts for ~78% of all skin cancer deaths. In the United States, the incidence of CMM has been increasing rapidly and currently, CMM is the 6th and 7th most commonly diagnosed cancer among men and women, respectively.¹ According to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, the estimated incidence of CMM in the United States in 1973 was 6.8 per 100,000 person-years, and this rate increased to 20.8 per 100,000 in 2005.² This increase in incidence is among the highest in SEER, with the exception of lung cancer in women. There are four major histologic subtypes of CMM. Superficial spreading melanoma (SSM) is the most common subtype, accounting for approximately 70% of cases, and occurs most often on the trunk. Nodular melanoma (NM) accounts for ~15% of melanomas and has only a vertical growth phase. Lentigo maligna melanoma (LMM) accounts for 13% of melanomas and correlates with long-term sun exposure in fair-skinned older individuals. Acral lentiginous melanoma (ALM) occurs predominantly on the nailbeds, palms and soles.^{2,3}

ALM accounts for about 2-3% of all melanomas.^{2,3} The overall incidence of CMM in darker-skinned individuals is low compared to Whites; however, ALM comprises a much higher proportion of CMM in darker-skinned individuals (i.e., Blacks, Asians, and Hispanics). In 1976, RJ Reed first described ALM as “pigmented lesions on the extremities, particularly on plantar regions, like the palms of the hands and soles of the feet, that are characterized by a lentiginous (radial) growth phase evolving over months or years to a dermal (vertical) invasive stage.”⁴ This was in contrast to CMM overall, which is generally found on sun-exposed areas. Reed was also the first to note that this type of melanoma was the most common expression of melanoma in blacks, and that patients with ALM had a very poor prognosis.⁵ In Reed's study, ALM patients had an average three-year survival rate of 11%. The poor survival rate of ALM patients may have been due in part to delays in diagnosis.

Several single institution case series of ALM have been published.^{6,7,8,9,10,11} However, since this subtype of melanoma is rare, these studies have been limited by small sample sizes and have not been population-based. There have been recent population-based studies on CMM overall in ethnic populations.^{12,13,14} However, these studies have not focused specifically on ALM and its incidence and survival patterns. Hence, the purpose of this study was to conduct a population-based evaluation of ALM to determine its current incidence and survival patterns in the United States. We also examined ALM tumor characteristics, such as tumor thickness and stage, which might affect prognosis.

Methods

We used the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute to derive incidence, frequency, and survival data for 1,413 histologically confirmed invasive cases of ALM reported to 17 cancer registries from 1986-2005.² Beginning in 1986, consistent data on ALM were available from 17 population-based registries that together represent approximately 26% of the US population. The 17 registries include 11 states (Alaska, Greater California, Connecticut, Rural Georgia, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah) and six standard metropolitan areas (Atlanta, Detroit, Los Angeles, San Francisco-Oakland, San Jose-Monterey, and Seattle-Puget Sound). SEER coverage includes approximately 23% of Whites/Caucasians, 23% of African Americans, 40% of Hispanics, 42% of American Indians and Alaska Natives, 53% of Asians, and 70% of Hawaiian/Pacific Islanders in the U.S.² Cases were identified using the World Health Organization's International Classification of Diseases for Oncology, Version Three (ICD-

O-3) morphology code for ALM (8744/3).¹⁵ All patients reported to SEER had their tumors confirmed histologically.

We calculated age-adjusted (2000 US standard) incidence rates using the SEER*Stat software public use program version 6.3.5;¹⁶ incidence rates were expressed as new cases per 1,000,000 person-years and were analyzed by age, gender, race, anatomical site of presentation, year of diagnosis, melanoma thickness, and stage at diagnosis. ALM incidence and frequency data were compared to CMM overall (n=88,885), which included all other melanoma histologic subtypes reported to SEER. The melanoma histologic subtypes in the CMM category included superficial spreading, nodular, lentigo maligna, balloon cell, amelanotic, desmoplastic, mucosal lentiginous, mixed epitheloid/spindle cell, epitheloid, and spindle cell melanomas.

Tumors designated as ALM were not included in the CMM category. Melanomas classified as “not otherwise specified (NOS)” (ICD-O-3 code 8720/3, n=71,099) were excluded from the analyses. Exclusion of the “NOS” melanomas had no statistically significant effects on the results (data not shown). Because of small numbers of ALM, American Indians and Alaska Natives (n=11) and patients designated as “unknown” race (n=17) were excluded from the study. Anatomic sites of presentation were compiled according to ICD-O-3 topography codes. Specific sites included skin of the upper limb, including the hand, (C44.6) and skin of the lower limb, including the feet (C44.7). All other anatomic sites of ALM reported to SEER (n=74) were excluded from this study.

Breslow thickness is a continuous variable and is the most important prognostic factor in cutaneous melanoma.^{17,18} Tumor thickness as measured by the Breslow technique was divided into the following four categories: 0.01-1.00 mm, 1.01-2.00 mm, 2.01-4.00 mm, and >4.00 mm. SEER thickness data were available only for tumors diagnosed after 1988. SEER extent of disease information determined stage of disease at diagnosis.^{13,19,20,21} Stage at diagnosis was defined according to the American Joint Committee on Cancer (AJCC) staging system.²⁰ Only those patients with adequate pathology information were selected for stage analyses. Melanoma patients with tumor sizes <1.0mm with or without ulceration or tumors <2.0mm without ulceration were coded as Stage I. Tumors >1.0mm with ulceration and nonulcerated tumors >2.0mm were coded as Stage II. Tumors of any size with positive regional lymph node involvement were coded as Stage III. Tumors of any size with metastatic involvement were coded as Stage IV.

Cause-specific survival is a measure of net survival that is calculated by using the cause of death listed on the death certificate to estimate the proportion of deaths due to a cancer. For these analyses, melanoma-specific survival rates were calculated using the survival module of the SEER*stat software version 6.3.5.¹⁶ Five- and ten-year melanoma-specific survival rates were calculated. Standard SEER exclusion criteria for the survival analyses included diagnosis of other cancers prior to diagnosis of ALM and missing survival information.

Time trends were evaluated with the use of SEER*stat software version 6.3.5,¹⁶ using incidence rates per 1,000,000 age-adjusted to the 2000 US Standard Population. Ninety-five percent confidence intervals (95% CIs) for incidence rates and trends were calculated using Tiwari's modification.²² Annual percentage change over time (APC) was calculated using weighted least squares method. The measures of association between incidence rate and race were analyzed through PROC FREQ of SAS (Version 9.1.3 of Windows), using Pearson's chi-square test. Results with $p < 0.05$ were regarded as significant. All statistical tests were two sided. Kaplan-Meier estimates were used to compare survival between different racial groups. PROC LIFETEST of SAS (Version 9.1.3) was used to test for differences in survivor function using the Wilcoxon test.

Results

Incidence and demographic data

Microscopically confirmed ALM was diagnosed in 1,413 residents of 17 SEER registry areas between 1986 and 2005, compared to 88,885 residents with CMM overall (excluding NOS). The proportion of ALM among all melanoma subtypes was greatest in people of color (Figure 1), accounting for 36% of all CMM in Blacks, 18% in Asian/Pacific Islanders, 9% in Hispanic Whites, and only 1% in Non-Hispanic Whites. The overall age-adjusted incidence rate of ALM for the SEER 17 cancer registries was 1.8 per 1,000,000 person-years. The incidence rates for the other major melanoma histologic subtypes were as follows: 12.0 per 1,000,000 person-years for LMM, 12.7 per 1,000,000 person-years for NM, 57.4 per 1,000,000 person-years for SSM.

The incidence rates of ALM in men and women were similar (1.9 and 1.8 per 1,000,000 person-years, respectively). Interestingly, the incidence rates for ALM were similar in Non-Hispanic Whites and Blacks, (1.8 per 1,000,000 person-years). Hispanic Whites had statistically significant higher incidence rates of ALM (2.5 per 1,000,000 person-years, $p=0.007$) compared to Non-Hispanic Whites. Asian/Pacific Islanders had statistically significant lower incidence rates of ALM (1.1 per 1,000,000 person-years, $p=0.002$) compared to Non-Hispanic Whites.

The mean age at diagnosis for ALM was 62.8 years, as compared to 58.5 years for CMM overall. The mean age at ALM diagnosis for men was 63.1 years, and for women, 62.2 years. Incidence also significantly increased with each year of advancing age, from 0.1 per 1,000,000 person-years in adolescents (<20 years old) to 9.3 per 1,000,000 person-years in the elderly (80-84 years old), with a yearly percentage change of 6.0 ($p<0.05$). Incidence also increased with each year of advancing age in both males and females (Figure 2A). Males had a yearly percentage change of 8.3 ($p<0.05$), and females had a yearly percentage change of 5.0 ($p<0.05$). The male age-specific incidence rates nearly doubled that of females after age 80. The increase in incidence with each year of advancing age was also seen across the different racial groups (Figure 2B), with Hispanic White age-specific rates nearly doubling that of Non-Hispanic Whites and tripling the rate of Asian/Pacific Islanders after age 70.

SEER 13 data from the years 1992-2005 were used to look at temporal trends in ALM, since Hispanic origin was first systematically recorded in SEER in 1992. The incidence rate of ALM increased slightly from 1.6 per 1,000,000 person-years (95% CI 1.3-1.9) during 1992-1994 to 2.1 per 1,000,000 person-years (95% CI 1.8-2.5) for 2004-2005 ($p=0.02$). Figure 3 shows that rates for Hispanic Whites increased from 1992 to 1998. Non-Hispanic Whites, Hispanic Whites, and Blacks all increased in incidence after 2003, but this rise was not statistically significant ($p>0.05$). Asian/Pacific Islanders had the lowest incidence rates of the four racial groups throughout the time period.

Site Distribution

The majority of ALM (~78%) were found on skin of the lower limb. Twenty two percent of ALM were found on skin of the upper limb. These percentages were similar in males and females, with 76% of ALM found on the lower limb in males, and 80% in females. Among racial groups, Blacks had the highest percentage of ALM occurring on the lower limb (84%), followed by Hispanic Whites (83%), Asian/Pacific Islanders (78%), and Non-Hispanic Whites (77%). In contrast, for CMM overall, the majority of tumors were found on the trunk (38.7%), followed by upper limbs (24.0%), lower limbs (22.4%), and head and neck (11.7%). The anatomic sites for CMM were also sex-dependent, with the majority of CMM occurring on the trunk in men (47.4%) and the lower limbs in women (35.9%). Among racial groups, the most frequent location for CMM were on the lower limbs in Blacks (64.0%), Asian/Pacific Islanders

(46.7%), and Hispanic Whites (36.4 %). By contrast, CMM occurred more frequently on the trunk (38.9%) in Non-Hispanic Whites.

Characteristics of Tumors

Since tumor thickness is the most important prognostic indicator in all types of melanoma, we evaluated tumor thickness for CMM and ALM. Overall, CMM were thinner than ALM, with 70% of CMM diagnosed at 0.01-1.00 mm. In contrast, for ALM, only 41% were diagnosed at 0.01-1.00mm and 37% were diagnosed at >2.00 mm (Table 1). Tumor thickness at diagnosis varied by sex. Males (45%) were more likely than females (31%) to have ALM diagnosis at >2.00mm, whereas more females than males tended to have 0.01-1.00mm tumors at diagnosis (46% and 36%, respectively). Non-Hispanic Whites had the highest percentage of thin ALM, with 43% diagnosed at 0.01-1.00 mm. The highest percentage of thick ALM (>4.00mm) was seen in Asian/Pacific Islanders (22%) (Table 2).

We also compared stage at diagnosis, another important prognostic indicator, among ALM and CMM. Approximately 38% of ALM were Stage I, in contrast to 68% of CMM (Table 1). In males, 30% of ALM were diagnosed at Stage I compared to 42% in females. This distribution by stage among males and females was significantly different ($p<0.001$, data not shown). As expected, similar to the patterns observed for tumor thickness, Non-Hispanic Whites had the highest percentage of ALM diagnosed at Stage I (40%), and Asian/Pacific Islanders had the highest percentage of ALM diagnosed at Stage III (50%) (Table 2).

Survival

Overall, patients with ALM had 5- and 10-year melanoma-specific survival rates of 80.3% (95% CI, 77.6-83.0) and 67.5% (95% CI, 63.4-71.6), respectively. These rates were lower than for CMM overall, which had 5- and 10-year survival rates of 91.3% (95% CI, 91.1-91.5, $p<0.001$) and 87.5% (95% CI, 87.1-87.9, $p<0.001$), respectively (Table 1, Figure 4A). When controlled for thickness, ALM 10-year survival rates at 0.01-1.00mm and 2.01-4.00mm were significantly lower than respective CMM 10-year survival rates (Table 1). When controlled for stage, ALM 10-year survival rates at Stages II and III were also significantly lower than respective CMM 10-year survival rates (Table 1). Females had statistically significantly higher 5- and 10-year melanoma-specific survival rates than males (85.6%, [95% CI 82.3-88.9], and 76.2%, [95% CI 71.3-81.1] compared to 73.8%, [95% CI 69.3-78.3], $p<0.001$ and 56.7%, [95% CI 49.8-63.6], $p<0.001$). However, when we controlled ALM for tumor thickness or stage, there was no statistically significant difference between 5- and 10-year survival rates among males and females (data not shown).

5- and 10-year melanoma-specific survival rates for ALM were highest in Non-Hispanic Whites (82.6% and 69.4%), intermediate in Blacks (77.2% and 71.5%), and lowest in Hispanic Whites (72.8% and 57.3%) and Asian/Pacific Islanders (70.2% and 54.1%) (Table 2, Figure 4B). However, when we controlled ALM for tumor thickness or stage (Table 2), there were no statistically significant differences between 5- and 10-year survival rates among the different racial groups (all p -values>0.05, data not shown).

Discussion

ALM is the least frequent of the four major histologic subtypes of CMM overall; however, it is a higher percentage of total melanoma in people of color. ALM was first described in the late 1970's and not documented by SEER as a distinct melanoma histologic subtype until 1986. The distinct histologic and phenotypic characteristics of ALM, in conjunction with its higher proportion of melanoma subtypes in Blacks, Hispanics, and Asians, has fostered speculation that this histologic variant of melanoma might differ biologically from its counterparts.

However, accurate assessment of ALM in the United States has been difficult because ALM accounts for such a small proportion of melanomas.²³ This study is the largest population-based evaluation of ALM yet conducted. We provide new data, particularly in Hispanic Whites and Asian/Pacific Islanders, on current incidence and survival patterns in the United States.

The proportion of ALM among all melanoma subtypes was greatest in people of color, with Blacks having the highest percentage (36%). These results are in contrast to former studies showing that SSM was the most common histologic subtype for all racial groups, including Blacks.^{12,13} It is important to note that our study included all SEER registry areas, representing approximately 26% of the US population. We also include the latest data from the years 2004 and 2005. Zell et al showed trends for melanoma in the state of California from 1993-2003, representing ~12% of the US population.¹³ Cormier et al showed trends for melanoma in the SEER 11 registries from 1992-2002,¹² representing ~14% of the US population.

The incidence of ALM in the United States has remained relatively steady over time, unlike CMM overall, where the incidence has been steadily increasing. During the 1970's, the incidence rate of CMM increased rapidly by about 6% per year.¹ Since 1981, the rate of increase has slowed to 1 to 3% per year. The steady increase in CMM incidence is most likely due to increased ultraviolet radiation, even though increased surveillance, physician and patient education, and sun safety measures have dramatically slowed the rate of increase. Our study showed that the incidence of ALM increased slightly from 1.6 to 2.1 per 1,000,000 person years from 1992 to 2005. This increase is most likely a result of ALM being recognized as a separate histologic subtype of melanoma in the mid 1980's and represents an overall increase in diagnosis. The incidence rate for ALM was similar in Non-Hispanic Whites and Blacks, but statistically lower in Asian/Pacific Islanders. Interestingly, Hispanic Whites had statistically higher incidence rates of ALM. In a recent population-based study of invasive melanoma in Hispanics, Cockburn et al reported an increasing incidence rate of CMM overall in the Hispanic population of California.¹⁴ Given our results and the increasing rate of melanoma overall in Hispanic populations, education campaigns should also provide information on ALM, particularly because of its atypical locations.

Melanoma in people of color has been shown to have a predilection for acral locations, especially on plantar regions.^{7,12,24} This also appeared to be true in our study in which the most frequent locations for ALM were on the lower limbs in all racial groups. This predilection for ALM on plantar locations has led many to believe that trauma may be important in the etiology for ALM, since sun exposure has not been shown to be a risk factor for ALM.^{8,25} The majority of ALM are found on the lower limbs, even though the surface area of the palms and soles is similar. The sole of the foot is constantly exposed to pressure, friction, maceration, and irritation.⁸ In two retrospective ALM case series where a trauma history was taken, 13% of 119 patients²⁵ and 25% of 35 patients⁷ reported prelesional trauma (ie—puncture wounds, stone bruises, friction blisters, contact dermatitis). Arguments against the trauma theory include the fact that the hand is exposed to more UV light and acute trauma.⁸ Furthermore, no change in incidence of melanoma of the soles was seen when African tribes became urbanized and began to wear shoes.^{7,26,27,28} Another factor that may play a role in the predilection of ALM for plantar locations is the fact that the density of melanocytes is 50% higher there than on the palm.⁸

Thickness and stage are important prognostic indicators for melanoma.^{12,17,18,21} Overall, about 70% of CMM were thin (0.01-1.00 mm) at diagnosis, and 68% were Stage I. In contrast, only 41% of ALM were classified as thin, and 38% were Stage I. ALM had significantly poorer melanoma-specific survival rates when compared to CMM overall. The distribution of thickness and stage at diagnosis between ALM and CMM may account for a large part of the survival differences. Interestingly, when controlled for thickness, ALM 10-year survival rates

for tumors <1.00mm and those 2-4.00mm were still ~10-20% lower than for CMM overall. When controlled for stage, ALM 10-year survival rates for tumors at Stages II and III were 10-15% lower than for CMM overall. The lower survival rates seen in ALM may be secondary to reported different biological characteristics of the melanoma subtypes. It has been suggested that there are different genetic pathways in the development of melanoma.²⁹ ALM have been reported to have significantly lower frequencies of BRAF mutations, which are often found in melanomas from intermittent sun exposure (ie—SSM or NM).^{30, 31} Furthermore, one study suggested that ALM are unique, in that they have constitutive activation of the phosphatidylinositol 3 kinase signaling pathway.³² Another suggested that ALM are characterized by focused gene amplifications occurring early in tumorigenesis, and malignant cells are present beyond the histologically detectable boundary, thereby revealing one mechanism of local recurrence.³³ Although these differences specific to ALM have been reported, they may not necessarily translate into survival differences; hence, the exact cause remains unknown.

Gender differences were also present in the distribution of ALM thickness and stage. Females had significantly higher percentages of Stage I and thin melanomas, while males had higher percentages of Stage III and thick melanomas. The distribution of tumor stage and thickness may also explain survival differences in males and females, since females had statistically significantly higher survival rates than males. When we adjusted for thickness or stage, there were no statistical differences in survival rates between males and females. Similarly, male patients with CMM overall have also been shown to have poorer survival rates relative to female patients in other studies, with increased tumor thickness at diagnosis being implicated as a causal factor.^{34,35}

Non-Hispanic Whites had the highest percentage of thin and Stage I ALM, whereas Asian/Pacific Islanders had the highest percentage of Stage III and thick (>4.00 mm) ALM. Hispanic Whites also had high percentages of Stage III tumors. This distribution of ALM tumors may partly explain survival discrepancies among the different racial groups, since Asian/Pacific Islanders and Hispanic Whites also had the lowest survival rates. These results are consistent with previous results by Cormier et al who showed that minority populations had lower melanoma survival rates secondary to advanced stage presentation.¹² When controlled for thickness or stage, there were no statistical difference between 5- and 10-year melanoma-specific survival rates in the different racial groups. These results are similar to previous studies that showed, after controlling for stage, similar survival rates among different racial groups with ALM.^{12,23,36,37}

Our study had several limitations. Approximately 50% of the melanoma cases in the SEER database were classified histologically as “not otherwise specified,” and therefore excluded from the analyses. Reporting of melanomas as “NOS” has been a common problem and data limitation in SEER-based analyses.³⁸ Exclusion of the “NOS” melanomas, however, had no statistically significant effects on the results. Furthermore, 74 tumors coded as ALM were reported to be located in anatomic sites other than the upper limbs and lower limbs. These tumors were excluded from the analyses, given their inconsistency with the definition of ALM. In addition, data was extremely limited for AJCC staging for ALM, with only ~60% of cases available for stage analyses. Finally, we used SEER data for this study. We had no information on socioeconomic status and access to health care, and therefore we were unable to examine these issues in the current study. These factors have been shown to be important for evaluating disparities in cancer survival and health care overall for minorities.^{12,13}

Conclusion

We have shown that ALM has specific epidemiologic characteristics that differ from other types of melanoma. It occurs later in life and on specific palmoplantar locations unattributable

to sunlight, unlike other melanoma subtypes.³⁹ Population-based data also showed that the incidence of ALM is similar in Non-Hispanic Whites and Blacks. Hispanic Whites have higher incidence rates of ALM, while Asian Pacific Islanders had lower incidence rates. ALM is a frequent melanoma histologic subtype in people of color, with Blacks having the highest percentage. Population-based data also showed that ALM is associated with a worse prognosis than CMM overall. ALM thickness and stage correlated with survival in gender and the four racial groups evaluated. Asian/Pacific Islanders and Hispanic whites had lower survival rates than other groups, and factors such as increased tumor thickness and more advanced stage at presentation are the most likely explanations. The reasons for delayed diagnosis require future study. Even though ALM is rare, given its atypical locations and poor survival rates, it is important that physicians maintain a high index of suspicion in all ethnic groups and closely examine a patient's palms, soles, and nailbeds.

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References

1. American Cancer Society. Cancer Facts & Figures 2008. Atlanta: American Cancer Society; 2008.
2. Surveillance, Epidemiology and End Results (SEER) Program. National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch; Apr. 2008 SEER*Stat Database. (www.seer.cancer.gov)
3. Markovic SN, Erickson LA, Rao RD, et al. Malignant Melanoma in the 21st Century, Part 1: Epidemiology, Risk Factors, Screening, Prevention, and Diagnosis. *Mayo Clin Proc* 2007;82:364–380. [PubMed: 17352373]
4. Reed, RJ. New Concepts in Surgical Pathology of the Skin. New York: John Wiley & Sons; 1976. p. 89-90.
5. Arrington JH, Reed RJ, Ichinose H, Krentz ET. Plantar lentiginous melanoma: A distinctive variant of human cutaneous malignant melanoma. *Am Journal of Surgical Pathology* 1977;1(2):131–143.
6. Rippey JJ, Lewin JR. Acral Lentiginous Melanoma or Hutchinson's Melanotic Freckle of the Extremities. *SA Medical Journal* 1978;53(26):1076–1077.
7. Coleman WP, Philip RL, Reed RR, Krentz ET. Acral Lentiginous Melanoma. *Arch Dermatol* 1980;116:773–776. [PubMed: 7396539]
8. Feibleman CE, Stoll H, Maize JC. Melanomas of the palm, sole, and nailbed: a clinicopathologic study. *Cancer* 1980;46(11):2492–504. [PubMed: 7438021]
9. Kuchelmeister C, Schaumburg-Lever G, Garbe C. Acral cutaneous melanoma in Caucasians: clinical features, histopathology and prognosis in 112 patients. *British Journal of Dermatology* 2000;143:275–280. [PubMed: 10951133]
10. Paladugu RR, Winberg CD, Yonemoto RH. Acral Lentiginous Melanoma: A Clinicopathologic Study of 36 Patients. *Cancer* 1983;52:161–168. [PubMed: 6850538]
11. Jimbow K, Takahasi H, Miura S, Ikeda S, Kukita A. Biological behavior and natural course of acral malignant melanoma. *Am J of Dermatopathology* 1984;6(1):43–53.
12. Cormier JN, Xing Y, Ding M, et al. Ethnic Differences Among Patients with Cutaneous Melanoma. *Arch Internal Medicine* 2006;166:1907–1914.
13. Zell JA, Cinar P, Mobasher M, Ziogas A, Meyskens FL, Anton-Culver H. Survival for Patients with Invasive Cutaneous Melanoma Among Ethnic Groups: The Effects of Socioeconomic Status and Treatment. *J Clin Oncol* 2008;26:66–75. [PubMed: 18165642]
14. Cockburn MG, Zadnick J, Deapen D. Developing Epidemic of Melanoma in the Hispanic Population of California. *Cancer* 2006;106:1162–68. [PubMed: 16429450]

15. Percy, C.; Fritz, A.; Ries, L., editors. Conversion of Neoplasms by Topography and Morphology from the International Classification of Diseases for Oncology, Second Edition (ICD-O-2) to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). Bethesda, MD: Cancer Statistics Branch, DCCPS, Surveillance, Epidemiology and End Results Program, National Cancer Institute; 2001.
16. Surveillance Research Program, National Cancer Institute. SEER*Stat software. (www.seer.cancer.gov/seerstat) version 6.3.5
17. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg* 1970;172:902–908. [PubMed: 5477666]
18. Markovic SN, Erickson LA, Rao RD, et al. Malignant Melanoma in the 21st Century, Part 2: Staging, Prognosis, and Treatment. *Mayo Clin Proc* 2007;82:490–513. [PubMed: 17418079]
19. Balch CM, Soong SJ, Gershenwalk JE, et al. Prognostic factors analysis of 17,600 patients with melanoma: Validation of the American Joint Committee on Cancer Melanoma Staging System. *J Clin Oncol* 2001;19:3622–3634. [PubMed: 11504744]
20. Balch CM, Buzaid AC, Soong SJ, et al. Final version of the American Joint Committee on Cancer Staging System for Cutaneous Melanoma. *J Clin Oncol* 2001;19:3635–3648. [PubMed: 11504745]
21. Gimotty PA, Botbyl J, Soong SH, Guerry D. A population-based validation of the American Joint Committee on Cancer Melanoma Staging System. *J Clin Oncol* 2005;23:8065–8075. [PubMed: 16258105]
22. Fay MP, Tiwari RC, Feuer EJ, Zou Z. Estimating average annual percent change for disease rates without assuming constant change. *Biometrics* 2006;62:847–854. [PubMed: 16984328]
23. Ridgeway CA, Hieken TJ, Ronan SG, Kim DK, Gupta TK. Acral Lentiginous Melanoma. *Arch Surg* 1995;130:88–92. [PubMed: 7802583]
24. Slingluff CL, Vollmer R, Seigler HF. Acral melanoma: A Review of 185 Patients with Identification of Prognostic Variables. *Journal of Surgical Oncology* 1990;45:91–98. [PubMed: 2214797]
25. Phan A, Touzet S, Dalle S, Ronger-Salve S, Balme B, Thomas L. Acral Lentiginous Melanoma: a clinicoprognostic study of 126 cases. *British Journal of Dermatology* 2006;155:561–569. [PubMed: 16911282]
26. Shah JP, Goldsmith HS. Malignant melanoma in the North American Negro. *Surg Gynecol Obstet* 1971;133:437–439. [PubMed: 5571164]
27. Rippey, JJ.; Schmanan, A. Skin tumors of Africans. In: Marshall, J., editor. *Essays on Tropical Dermatology*. Amsterdam: Excerpta Medica; 1972. p. 98-115.
28. Kaplan I, Youngleson J. Malignant melanomas in the South African Bantu. *Br J Plast Surg* 1972;25:65–68. [PubMed: 5008787]
29. Curtin JA, Fridlyand J, Kageshita T, et al. Distinct Sets of Genetic Alterations in Melanoma. *N Engl J Med* 2005;353:2135–2147. [PubMed: 16291983]
30. Maldonado JL, Fridlyand J, Patel H, et al. Determinants of BRAF Mutations in Primary Melanomas. *J Nat Cancer Inst* 2003;95:1878–1880. [PubMed: 14679157]
31. Viros A, Fridlyand J, Bauer J, et al. Improving Melanoma Classification by Integrating Genetic and Morphologic Features. *PLoS Medicine* 2008;5:e120. [PubMed: 18532874]
32. Muchemwa FC, Ma D, Inoue Y, et al. Constitutive activation of the phosphatidylinositol 3 kinase signaling pathway in acral lentiginous melanoma. *Br J Dermatol* 2008;158:411–413. [PubMed: 17999703]
33. Bastian BC, Kashani-Sabet M, Hamm H, et al. Gene Amplifications Characterize Acral Melanoma and Permit the Detection of Occult Tumor Cells in the Surrounding Skin. *Cancer Research* 2000;60:1968–1973. [PubMed: 10766187]
34. Scroggins CR, Ross MI, Reintgen DS, et al. Gender-Related Differences in Outcome for Melanoma Patients. *Annals of Surgery* 2006;243:693–700. [PubMed: 16633005]
35. Lasithiotakis K, Leiter U, Meier F, et al. Age and Gender are Significant Independent Predictors of Survival in Primary Cutaneous Melanoma. *Cancer* 2008;112:1795–1804. [PubMed: 18306371]
36. Cascinelli N, Zurrida S, Galimberti V, et al. Acral Lentiginous Melanoma. *J Dermatol Surg Oncol* 1994;20:817–822. [PubMed: 7798414]

37. Leffall LD, Krementz ET, Sutherland CM, Carter RD, et al. Malignant Melanoma in the American black. *Ann Surg* 1976;(183):533–542. [PubMed: 1275593]Discussion, from
38. Howe HL, Wu X, Ries L, et al. Annual Report to the Nation on the Status of Cancer, 1975-2003, Featuring Cancer Among U.S. Hispanic/Latino Populations. *Cancer* 2006;107:1711–42. [PubMed: 16958083]
39. Kuchelmeister C, Schaumburg-Lever G, Garbe C. Acral cutaneous melanoma in Caucasians: clinical features, histopathology and prognosis in 112 patients. *Br J Dermatol* 2000;143:275–280. [PubMed: 10951133]

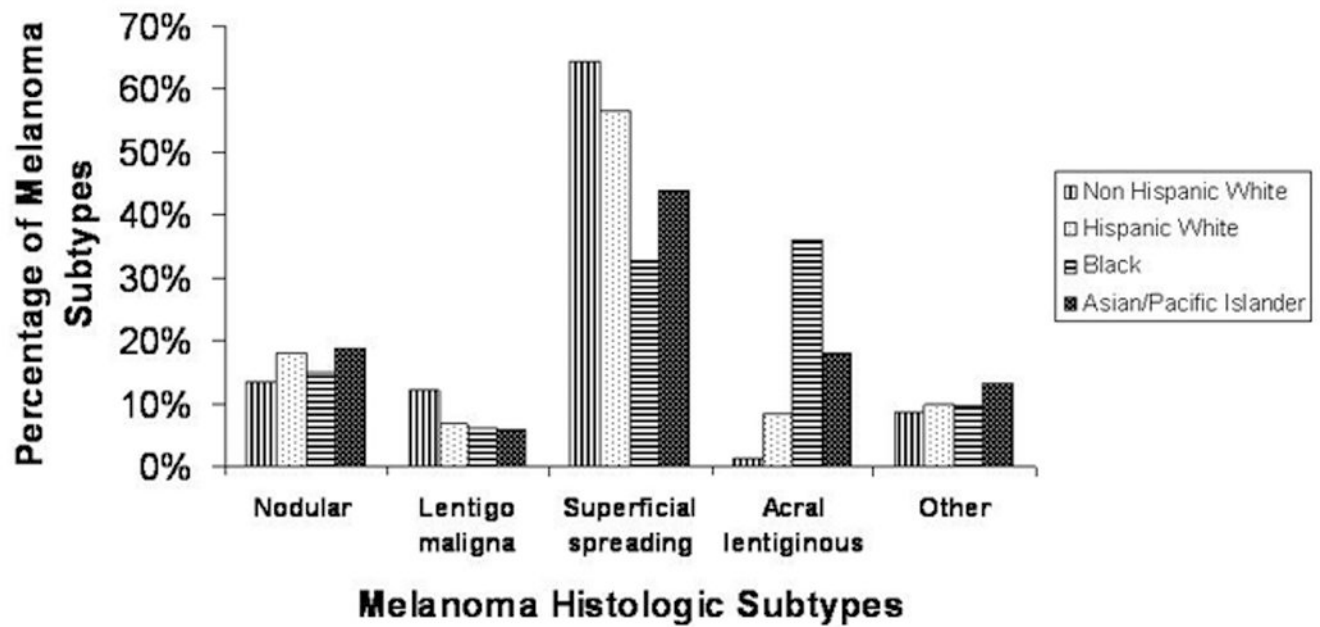


Figure 1.

Distribution of major melanoma histologic subtypes by race using SEER 17 registries, 1986-2005. "Other" includes all additional melanoma histologic subtypes coded by SEER, including balloon cell, amelanotic, desmoplastic, mucosal lentiginous, mixed epitheloid/spindle cell, epitheloid, and spindle cell melanomas.

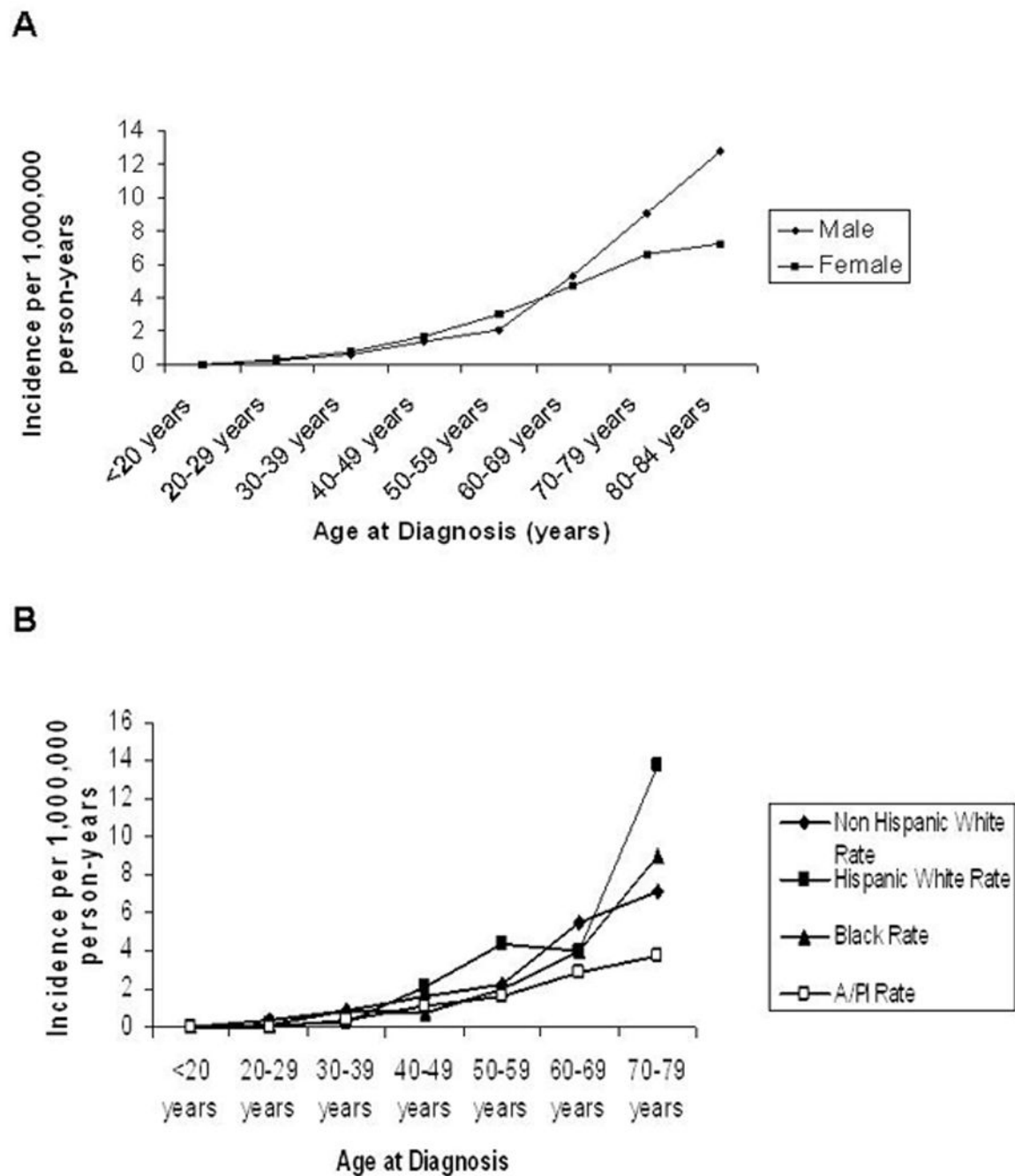


Figure 2.

Age-specific incidence rates of ALM by decade based on gender (2A) and race (2B). Incidence rates are based on the SEER 17 registries, years 2000 to 2005, and reported per 1,000,000 person-years and age-adjusted to the US 2000 standard.

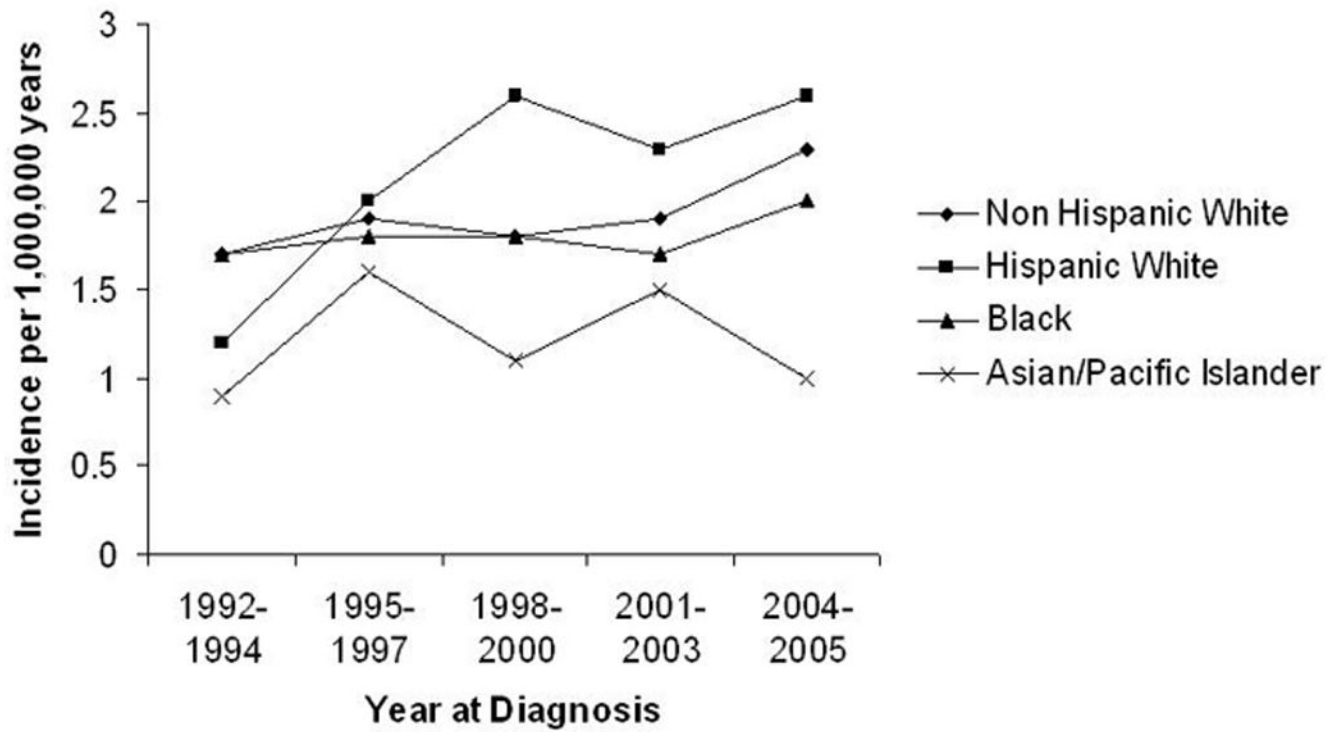
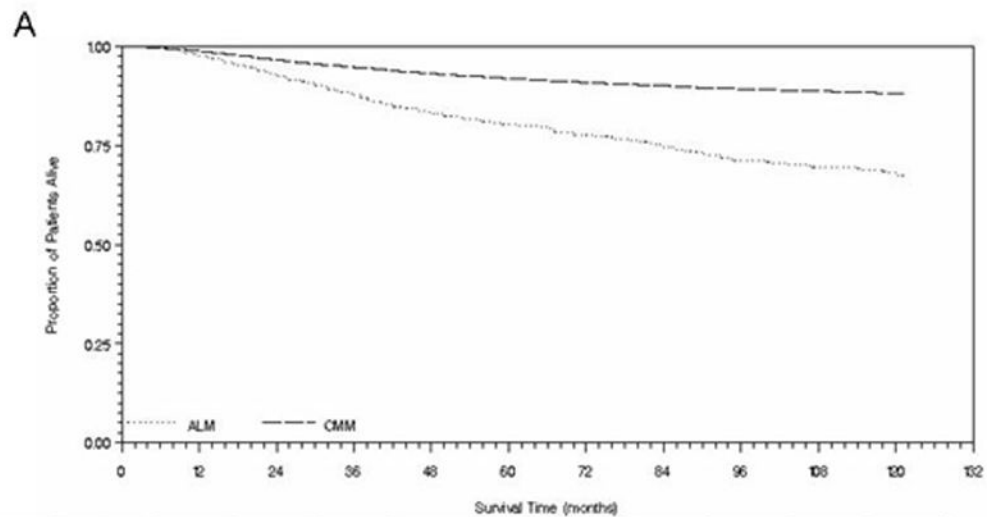
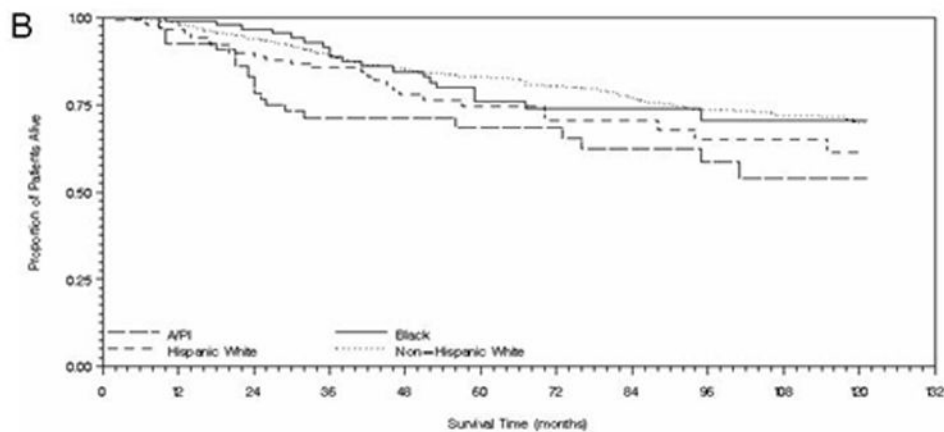


Figure 3.

Age-adjusted incidence rates of ALM by year of diagnosis based on race. Incidence rates are based on the SEER 13 registries (1992-2005) and reported per 1,000,000 person-years and age-adjusted to the US 2000 standard.



No. at risk	Baseline										
CMM	61,975	54,755	47,205	40,731	34,797	29,117	24,216	21,281	18,454	15,940	13,697
ALM	1,178	1,011	838	684	547	441	354	288	238	198	158



No. at risk	Baseline										
NHW	849	746	625	520	417	340	269	218	185	156	122
HW	151	116	89	68	48	38	30	23	19	15	11
Blacks	108	92	76	62	54	39	34	28	19	17	16
A/PI	70	57	48	34	28	24	21	19	15	10	9

Figure 4.

A) Melanoma-specific survival for CMM and ALM, SEER 17 (1986-2005). B) Melanoma-specific survival by race/ethnicity for ALM, SEER 17 (1986-2005). Survivals were evaluated using the Kaplan-Meier method (Wilcoxin test). These survival trends were not controlled for thickness and stage.

Table 1
5- and 10-year melanoma-specific survival rates^a (percentages) for CMM and ALM diagnosed in the SEER 17 (1986-2005) registries in the US based on tumor thickness and stage at diagnosis.

	CMM		ALM		CMM vs ALM Survival Rates					
	n	% ^c	5-Year Survival	10-Year Survival	n	% ^c	5-Year Survival	10-Year Survival	5-year p-value	10-year p-value
Overall	61,975 ^b	---	91.3	87.5	1178 ^b	---	80.3	67.5	<.001	<.001
0.01-1.00mm	37,629 ^d	70.0	97.4	95.4	422 ^d	41.3	95.5	87.8	.12	.01
1.01-2.00mm	8,440	15.7	88.7	81.6	221	21.6	87.3	81.2	.62	.93
2.01-4.00mm	4,995	9.3	72.8	62	241	23.6	69.6	43.5	.39	.001
4.00mm	2,663	5.0	58.2	49.1	137	13.4	51.4	36.0	.21	.06
Stage I	29,247 ^e	67.5	98.4	96.6	302 ^e	37.8	98.8	91.8	.57	.07
Stage II	8,777	20.2	86.8	78.5	221	27.6	85.8	68.2	.70	.04
Stage III	5,035	11.6	66.1	56.6	260	32.5	61.2	40.9	.17	.01
Stage IV	292	0.7	25.5	19.9	17	2.1	22.2	22.2	.77	.84

Abbreviations: CMM=cutaneous malignant melanoma, ALM=acral lentiginous melanoma

^aThe cause-specific survival rates are based on data from the Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: SEER 17 Registries, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch (April 2008).

^bStandard SEER exclusion criteria for the survival analyses included diagnosis of other cancer prior to diagnosis of melanoma and exclusion of patients for whom survival information was not available (n=26,910 for CMM; n=235 for ALM).

^cPercentage of tumors that are the specified thickness or stage.

^dSEER tumor thickness data available only for tumors diagnosed after 1988 (n=53,727 for CMM; n=1,021 for ALM).

^eOnly those patients with adequate pathologic information were selected for stage analyses (n=43,351 for CMM; n=800 for ALM).

Table 2

5- and 10-year melanoma-specific survival rates^a (percentages) by race for ALM diagnosed in the SEER 17 registries (1986-2005) in the US based on tumor thickness and stage at diagnosis.

	NHW		HW		Blacks		A/PI				
	n ^b (%)	5-Yr	10-Yr	n (%)	5-Yr	10-Yr	n (%)	5-Yr	10-Yr		
Overall	849 ^b	82.6	69.4	151	72.8	57.3	108	77.2	71.5	70.2	54.1
Thickness (mm)											
0.01-1.00	320 ^d (43.0)	96.5	87.4	52 (40.3)	92.0	84.9	34 (39.1)	91.0	91.0	16 (27.1)	92.9
1.01-2.00	161 (21.6)	86.4	81.6	33 (25.6)	88.3	58.9	17 (19.5)	88.9	88.9	10 (16.9)	100
2.01-4.00	172 (23.1)	72.1	43.9	31 (24.0)	50.9	50.9	18 (20.7)	79.5	51.1	20 (33.9)	67.1
>4.00	93 (12.5)	52.9	34.0	13 (10.1)	41.1	~	18 (20.7)	61.5	61.5	13 (22.0)	36.4
Stage											
I	238 ^e (40.1)	99.0	91.0	29 (31.5)	100	91.7	23 (34.8)	100	100	12 (25.0)	91.7
II	168 (28.3)	87.3	69.6	24 (26.1)	63.9	63.9	18 (27.3)	92.3	69.9	11 (22.9)	68.2
III	177 (29.8)	62.6	40.9	37 (40.2)	61.4	42.1	22 (33.3)	49.2	~	24 (50.0)	62.5
IV	11 (1.9)	~	~	2 (2.2)	~	~	3 (4.5)	~	~	1 (2.1)	~

Abbreviations: ALM=acral lentiginous melanoma, NHW=Non-Hispanic Whites, HW=Hispanic Whites, A/PI=Asian/Pacific Islanders

^aThe melanoma-specific survival rates are based on data from the Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: SEER 17 Registries, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch (April 2008).

^bStandard SEER exclusion criteria for the survival analyses included diagnosis of other cancer prior to diagnosis of melanoma and exclusion of patients for whom survival information was not available [n=235].

^cPercentage of tumors that are the specified thickness or stage.

^dSEER race-specific tumor thickness data available only for tumors diagnosed after 1988 (n=1,021).

^eOnly those patients with adequate pathologic information were selected for race-specific stage analyses. (n=800).

^fThere was not sufficient follow up data to produce a survival rate or meaningful survival analyses.