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Melanoma Arising in African-, Asian-, Latino- and Native-American Populations

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This review highlights melanoma trends observed among African-, Asian-, Latino- and Native-American populations. Melanoma is the most lethal form of skin cancer, accounting for about 75% of all skin cancer deaths. Generally, incidence rates increase with age, peak after age 40, and are greater in men than women. However, these trends do not reflect what is typically seen in minority ethnic groups, where incidence rates are lower. In addition, for some groups, relative disease-specific survival also is lower compared with European-Americans. Melanomas in minority populations also tend to appear in atypical locations and are of unclear etiology. To improve our understanding of the causes of melanoma arising in ethnic minority populations future research efforts are needed. In addition, the general lack of awareness of this disease entity among minority populations and the fact that certain ethnic groups tend to present with advanced disease further highlight the need for educational programs for both patients and health care professionals.
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Although melanoma affects individuals from all ethnic groups, the presentation, prognosis, and treatment options for this disease can differ. It is the third most-common skin cancer in African-, Asian-, and Latino-American groups. In comparison with people of mainly European descent living in America, the incidence of melanoma in ethnic minority populations is significantly lower, following a lower overall skin cancer rate. Melanomas that arise in African Americans (AA), Asian/Pacific Islanders (A/PI), Latino Americans (LA), and Native Americans (NA) are more frequently found on sun-protected skin. More specifically, such populations are more likely to develop malignant melanoma on acral, subungual, and mucosal skin. Unfortunately, because of their rarity and occult presentation, the diagnosis of these melanomas can be delayed.

On the basis of our clinical experience and review of the literature, we propose that there are several challenges in treating melanoma arising in ethnic minority populations. First, evidence has shown that some ethnic minority populations, when compared with European-American (EA) populations, present with later-stage disease and may even have more aggressive disease.[1] These trends ultimately contribute to decreased overall survival. Second, ethnic minority groups are disproportionately represented in urban cities and coastal regions and as a group are projected to become the US majority by 2050.[2] Therefore, the number of new melanoma cases arising from these groups will likely increase as the population increases. Finally, there have been molecular discoveries pertaining to melanoma subtypes common in ethnic minority groups. Physicians will be asked to effectively make use of these discoveries to provide genetically tailored treatment modalities. In light of the disease's current and future challenges, it is important to be aware of issues and trends seen in this potentially lethal disease.

Group Definitions and Study Populations

The standard repertoire of terms used to describe patient identity consists largely of race-based labels that have been shown to have little scientific merit. These terms have not always been used consistently in scientific and epidemiologic studies. Genomic studies have revealed that selected populations that have been geographically separated from one another throughout history exhibit significant genetic divergence, making geographic ancestry a potentially useful descriptor.[3] Below is a description of the terms used in this article and limitations encountered with specific groups. Generally, the authors prefer to use terms that specify biogeographical ancestry and current place of residence. When applicable, ethnic specific terms are used to denote social/cultural groups.

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The term AA describes people who self-identified as being of mostly African decent but are living in America. According to the US Census Bureau, the racial category "black" or "African American" refers to people having origins in any of the black racial groups of Africa. It should be understood, however, that this is an admixed population that also has European and NA ancestry. NA refers to the indigenous peoples of North, Central, and South America. This definition is synonymous with the racial categorization "American Indian" and "Alaskan Native" set by the US Census Bureau.

Many studies and cancer registries describe the A/PI racial/ethnic group. This is a heterogeneous group that has many genetically, ethnically, and culturally distinct subpopulations. According to the US Census Bureau, "Asian" refers to people having origins to any of the original peoples of the Far East, South-East Asia, or the Indian subcontinent. It includes people who indicated their race(s) as "Asian Indian," "Chinese," "Pakistani," or "Filipino." "Native Hawaiian" and "Other Pacific Islander" refer to people having origins in any of the original peoples of Hawaii or other Pacific Islands.[2] This article gives information about specific subpopulations within the A/PI group when available, because the incidence and presentation of melanoma among these subpopulations can differ.

The term LA refers to people having origins in any of the Spanish-speaking peoples of Central and South America. The terms Hispanic and Latino are used interchangeably by the US Census Bureau to identify people who indicate that they originate from a Spanish-speaking country.[2] However, a person of Hispanic origin may be of any race or heritage. Traditionally, Hispanic groups have European, Native-American, and African ancestries that vary regionally. The authors prefer the term LA because it indicates biogeographical ancestry as well as place of residence. In the United States, most (65%) LA people are of Mexican ancestry, and 23% are of other LA ancestry, followed by Puerto Rican (9%) and Cuban (3%).[2] The analysis of data for this group presents specific difficulties because many cancer registries use both surname and maiden name to impute race/ethnicity data when self-reported information is lacking. Therefore, when maiden names are not available, misclassification of true background may occur for women who acquire Spanish or non-Spanish surnames through marriage. Additionally, misclassification might occur for certain groups that have Spanish surnames and have not self-identified, ie, Filipinos.

The term EA describes people of mostly European origin that now reside in the United States. This article uses EA in place of the terms Caucasian, white, or non-Hispanic white. "White" is used by the US Census Bureau to refer to people having origins in any of the original peoples of Europe, the Middle East, or North Africa. It includes people who indicated their race as "white" or write in entries, such as Irish, German, Italian, Lebanese, Near Easterner, Arab, or Polish. It should be recognized that although the vast majority of the people within this group have origins in Europe, a small minority do not. In addition, some of these specific subpopulations have been shown to have variations in melanoma presentation and incidence.

General Trends

Compared with EA populations, US minority groups make up a relatively small percentage of patients who develop melanoma. According to Surveillance Epidemiology and End Result (SEER) population-based data from 2001 to 2005, the age-adjusted melanoma incidence per 100,000 persons was 22.6 for EA compared with 1.0, 1.4, 3.1, and 4.7 for AA, A/PI, NA, and LA, respectively. In 2008, an estimated 62,500 total individuals developed melanoma and, as a group, ethnic minorities represented <5% of all diagnosed cases. Data show that the incidence rate for melanoma is increasing for most, but not all, ethnic groups in the United States. An analysis of SEER data from 1996 to 2005 revealed that the melanoma incidence in A/PI and LA populations is increasing. However, the melanoma incidence in AA is decreasing. The average annual percent change (AAPC) from 1996 to 2005, was 2.8 for EA compared with −5.8%, 2.2%, and 1.3% for AA, A/PI, and LA groups, respectively.[4]

Overall, the incidence of melanoma among ethnic minority groups shows a peak between the ages of 50-60 and occurs more often in women. Cormier et al[5] compared SEER demographic characteristics among 49,772 patients with invasive melanoma from 1992 to 2002. Here the mean age at melanoma diagnosis was 57 years for EA, compared with 54 years for LA, 59 years for AA, 52 years for NA, and 57 years for A/PI ($P < 0.001$). Female sex represented a larger proportion of patients in minority populations than in the EA populations (50.6%-54.5% vs. 43.9%, respectively; $P < 0.001$).

The presentation of melanoma among minority groups when compared with EA groups also differs considerably in regards to primary site distribution, common histologic subtype, and stage at diagnosis. A comparison of the clinicopathologic characteristics by race/ethnicity found that the truncal region is the most common primary tumor site for NA, whereas the lower extremity is the most common primary site for LA, AA, and A/PI. Acral lentiginous melanoma (ALM) is more prevalent among minority populations than in EA: Odds ratios, 5.5, 20.5, 4.1, and 11.5 for LA, AA, NA, and A/PI respectively, respectively.[5] However, ALM is not necessarily the most common histologic subtype for all minority groups. In addition, ethnic minority populations are more likely to present with thicker, ulcerated lesions and have evidence of systemic disease.[5,6]

For the vast majority of melanoma subtypes that arise in ethnic minority populations the etiology is unknown with no established lifestyle, occupational or environmental risk factors. Although several factors have been implicated as potentially etiologic, findings are inconsistent.[7-9] By contrast, ultraviolet (UV) light is known to play a major role in the etiology of melanoma arising in people of mostly European ancestry. This may have significance for ethnic minority groups that have diverse ancestral backgrounds.

Group-Specific Information

AA

Compared with other major ethnic groups, people of African ancestry rarely develop melanoma. AAs exhibit a melanoma incidence rate of 1 per 100,000.[2] This relatively low incidence has been described within the United States and abroad. For example, in an analysis of patients treated at a South African major referral center between 1990 and 2001, the authors found that of 844 patients who presented with melanoma, 47 (5.6%) were indigenous Africans and 40 (4.8%) were of colored/mixed ancestry.[10]

Melanin is protective in the development of UV-induced carcinogenesis in darker-skinned persons. In the African Diaspora, when melanoma does occur, it usually develops in regions of the human body that are protected from the sun. More specifically, such populations develop malignant melanoma on acral, subungal, and mucosal sites and incidence rates for these areas vary.[5,6,10-13] The foot represents the most common site (Fig. 1). Byrd et al found that in 36 AAs diagnosed with melanoma, the foot was the most common primary site (38.9%). This finding is compared to 2.4% in EA, which were more likely to present with nonacral primary sites.[6] Similar findings have been reported by Hudson et al, who studied melanoma in native "black" South Africans.[14] The incidence of melanoma occurring on plantar surfaces appears similar in AAs and EAs. The relative lack of melanoma occurring in sun-exposed sites in AAs accounts for the higher percentage of acral primaries.[15]

Evidence also suggests that the EA to AA incidence ratio of other sun-protected melanomas is nearly equal. Mucosal melanomas, ie, melanomas that occur in the nasal cavity, oral cavity, and anorectal and genital tracts, account for only 1.4% of melanoma cases overall.[16] Studies have shown that the EA to AA incidence ratio for mucosal melanoma is low, ie, 2.2-2.3:1. However, the ratio for uveal melanoma in EA vs AA populations (18:1) resembles that of cutaneous melanoma (13:1 to 26:1). Surprisingly, the EA to AA ratio of conjunctival melanoma is only 2.6:1.[17] These findings suggest that one is almost as likely to find a mucosal (and conjunctival) melanoma in an AA as they are in an EA.

The most common histologic subtype of melanoma encountered in people of African decent is ALM.[6,12,14] It was so named because of its predilection for acral (nonhair bearing) areas of the body, particularly the palms, soles, and the subungal areas, and its distinct radial or "lentiginous" growth phase. ALM occurs with the same incidence in AA as it does in EA populations.[18,19] Evidence shows that ALM has a genomic profile different from other variants.[20-23] ALM has been shown to have a greater frequency of focused gene amplifications when compared with superficial spreading melanoma (SSM).[24] A small percentage of both ALMs and mucosal melanomas have been shown to harbor mutations in the KIT oncogene similar to gastrointestinal stromal tumors,[25] raising the possibility of targeted therapy with KIT inhibitors for these subtypes of melanoma. Whether KIT mutations differ by ethnic grouping is not known.

Evidence also shows that ALM is most probably related to specific cancer susceptibility but unrelated to familial melanoma and tendency to developing nevi or sun exposure.[26] Other major histologic subtypes, SSM, lentigo maligna melanoma (LMM), and nodular melanoma (NM), are also found in African-descended groups, albeit to a lesser degree compared with ALM. Another rare variant, desmoplastic melanoma, has been reported as well.[27] To our knowledge, nevoid melanoma and clear cell sarcoma are exceedingly rare in this group.

Of the reports regarding melanoma arising in people of African decent, several show a trend toward poorer overall survival.[6,9,12-14] The fact that this group tends to present with advanced stage disease is believed to contribute to this disparity. Byrd et al[6] examined AA patients in the Washington, DC, area. In this study, 32% of AA and 13% of EA were initially seen with regional and distant disease. The 5-year survival rate was 58.8% in AA compared with 84.8% in EA. Another study examined AAs residing in Miami-Dade County, Florida, from 1997 to 2001. Of the 1036 melanoma cases analyzed, 21 identified as AA (2.0%). Forty-eight percent of AA patients had regional or distant disease at presentation, compared with 22% of EA patients ($P = 0.015$).[28] Jemal et al, showed that AA, when compared with EA, are not only more likely to present with regional (23% vs. 13%) and distant (12% vs. 4%) disease but also show a decreased overall 5 year survival (77% vs. 92%). In this same study, AA were shown to be less likely to present with localized disease (58% vs. 80%).[29]

Although low socioeconomic status (SES) is usually an indicator of poor outcome, there are likely other factors that are contributing to the difference in survival. Zell et al[1] conducted a case-only analysis of California Cancer Registry (CCR) data from 1993 to 2003 and found that although low SES independently predicts poor outcome among patients with cutaneous melanoma, the poor survival observed for AA patients is not explained by differences in treatment or SES. It is likely that other factors, such as tumor biology, unfavorable primary sites, and histologic subtypes commonly encountered in this group are playing a major role.

LA

The melanoma incidence in nonwhite LA populations residing in the United States is 4.7 per 100,000.[4] This population, which is the fastest-growing population in the United States, shares many features with both AA and EA populations, a finding that parallels their intermediate skin pigmentation and admixed genetic background. Traditionally, LA groups have European, NA, and African ancestries that vary regionally.[30] Within the United States, LA might self-identify ethnically with being Hispanic but are of either "black" or "white" race.[28]

Overall the incidence of melanoma in LA individuals has continued to increase at an annual rate of 2.9% ($P < 0.05$) during the past 15 years, which is comparable with that in EA (3.0%).[31] An analysis of CCR data between 1988 and 2001 reported that the incidence primarily consists of an increase

in thicker melanomas.[32,33] When separated by skin pigmentation and region, melanoma incidence trends have been shown to vary. For example, past data have shown that fairer New Mexican Hispanics have a greater incidence of melanoma than darker Puerto Ricans.[34-36] However, studies have shown an increase in the incidence of melanoma among Puerto Ricans as well.[37]

To date, there are only a few published reports regarding data on the presentation of melanoma in LA. Cormier et al[5] analyzed SEER data for 11 areas (San Francisco/Oakland, Detroit, Atlanta, Seattle, Los Angeles County, San Jose/Monterey [CA], Connecticut, Iowa, New Mexico, Utah and Hawaii) from 1992 to 2002 and found that the lower extremity was the most common primary site for LA (30.0%). This information confirmed previous analyses of CCR data from 1988 to 1993 and Puerto Rican Cancer Registry data from 1981 to 1987.[11,35] In contrast, SEER data from 1973 to 1981 demonstrated that lighter-skinned New Mexican Hispanics tended to develop melanomas on the trunk in men and on the legs in women, similar to findings for EA.[34] Likewise, other variants of melanoma that have been described in EA can appear in LA (Fig. 2).

ALM is more prevalent among LA than EA (OR 5.5).[5] In a study that analyzed CCR data from LA and EA from 1998 to 2001, LA men were found to have a greater percentage of ALM lesions compared with their EA counterparts (5.1% vs. 0.6%). However the most common histologic subtype was SSM for both LA and EA (23.6% vs. 30.7%).[32] An analysis of darker Puerto Rican subjects also found that the most frequently recognized histologic type was SSM, followed by ALM, NM, and LMM.[35]

Unfortunately, despite a similar increase in incidence as EA populations, survival has not improved to the same degree for LA. LA have a decreased overall 5 year survival compared with EA.[5] Studies show that this is likely because LAs, similar to AAs, are more likely to present with advanced-stage disease.[11,38,39] Cockburn et al[32] found that intermediate-thickness tumors were seen in 24.4% of EA men compared with 35.4% in LA men. Hu et al[28] found late-stage (regional and distant) diagnosis was more common among LA (26%) patients compared with EA patients (16%) ($P < 0.001$).

It is likely that the decreased survival is largely the result of low SES. A previous analysis of CCR melanoma data from 1993 to 2003 that adjusted for age, sex, histology, stage, anatomic site, treatment, and SES showed no survival differences for LA compared with EA.[1]

A/PI

An analysis of SEER population-based data from 2001 to 2005 revealed a melanoma incidence among A/PI of 1.4 per 100,000. These incidence data are similar to those seen in AAs but reflects an average annual percentage increase of 2.2% from 1996 to 2005.[4]

Analyzing data for A/PI in the United States is difficult because this group encompasses a wide range of ethnic groups that are genetically, phenotypically, and culturally different. Many studies demonstrate that cancer incidence and mortality patterns among A/PI are heterogeneous, but national statistics on specific A/PI subpopulations are not routinely available. California has the largest Asian-American population of any state, and its 5 largest groups in order of population size include Chinese, Filipino, Vietnamese, Korean, and Japanese. The CCR reported the incidence of melanoma for Asians is 0.9 per 100,000 men and 0.8 per 100,000 women.[11] Abroad, studies reflect subtle differences. For example, the melanoma incidence in Asian Indian males is roughly 0.2 per 100,000. However, the melanoma incidence of Japanese males is 0.7 per 100,000 and has shown a steady increase since 1987.[40,41] Other studies have found regional pigmentation differences. For example, one study found that fairer-skinned Chinese in Singapore had a greater rate of melanoma than darker-skinned Singaporean Indians at 0.5 vs 0.2 per 100.000, respectively.[42]

Overall, the A/PI population tends to present with melanomas in specific regions that are also sun-protected. More specifically, such populations develop malignant melanoma on the extremities, primarily plantar acral sites (Fig. 3). Mucosal and subungual melanomas are also common sites. An analysis of SEER data from 1992 to 2002 identified 394 A/PI with primary invasive cutaneous melanoma. Among this group, the foot was the most common primary site at 36.8%.[5] This trend has been reproduced in native groups of Japan and China.[41,43,44] Collins[44] studied melanoma in Chinese people of Hong Kong from 1964 to 1982. Of the 43 primary cutaneous melanomas, 56% were in the foot, and 83% of these lesions occurred on the plantar surface. All the subungual tumors, with 1 exception, presented in the nail bed of the great toe or thumb.

A greater percentage of mucosal melanomas are known to occur in this group. In the Chinese population of Hong Kong, oral melanomas represented approximately 7.5%, and two thirds of these tumors arose from oral melanosis. Internal mucous membranes, along with the plantar foot, are also major anatomic sites for melanoma in Asian Indians.[45] For this group with mucosal melanomas of the head and neck, most of the tumors occur in the palate and alveolus.[46] Uveal and conjunctival melanomas occur, albeit rarely and at a similar incidence rate as that in AA.[16,17,47]

Among A/PI the most common histologic subtype is ALM, which also has been shown abroad in native peoples of China and Japan.[5,41,44] However NM, SSM, and LMM are also seen. Ishihara et al[41] studied native Japanese patients with melanoma from 1987 to 2000. ALM accounted for nearly 50% of the patients. Before 1997, NMs ranked second. However, during the past 3 decades the study noted a steady increase in SSM that eventually surpassed the incidence of NM. This increase in SSM is partly responsible for the overall increase in melanoma incidence noted in Japan.

Similar to their AA and LA counterparts, as a group A/PI tend to present with more advanced, thicker tumors that tend to have a poorer prognosis and a greater rate of mortality. Cormier et al[5] found that A/PIs when compared with EAs were less likely to present with thin melanomas, at rates of 48.7% vs. 66%, respectively. In addition A/PIs were more

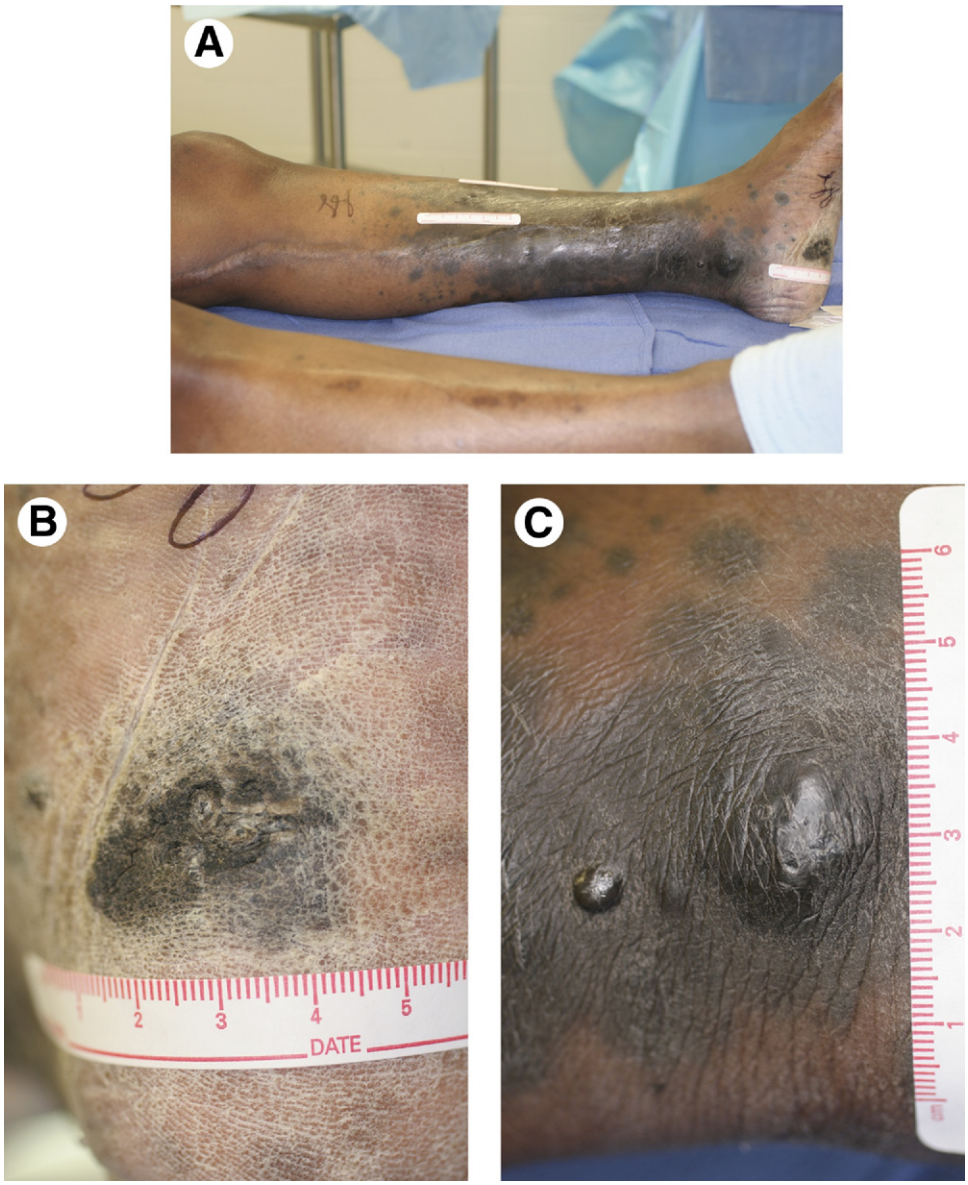

Figure 1 (A) Acral lentiginous melanoma primary with in-transit metastasis in an African-American man. Courtesy of Dr Stanley P. L. Leong. (B) Acral lentiginous melanoma primary of the plantar foot in an African-American man. Courtesy of Dr Stanley P. L. Leong. (C) In-transit metastasis in an African-American man. Courtesy of Dr Stanley P. L. Leong.

likely to have primary melanomas that were Clark level IV/V, ulcerated, and have advanced disease at presentation.

Various groups have reported a decreased 5-year overall survival for Asian populations.[5] It is likely that this decreased survival is caused largely by low SES. A previous analysis of CCR melanoma data from 1993 to 2003 that adjusted for age, sex, histology, stage, anatomic site, treatment, and SES showed no survival differences for Asians compared with EAs in the final analysis.[1] In addition although decreased survival has been shown for A/PI groups here in the United States, this is not necessarily the case abroad. Ishihara et al[41] reported the survival rates of native Japanese melanoma patients stratified by stage are mostly comparable with those for EA. In addition, within this same study the survival rates in stage II and III appeared slightly higher for native Japanese patients.

NA

According to SEER data from 2001 to 2005, the age-adjusted melanoma incidence per 100,000 persons was 3.1 for NA. This is slightly lower than that recorded for LA but greater than that recorded in AA and A/PI.[4] Unfortunately, there is a lack of comprehensive data regarding skin cancer in NA. Not only is there a relatively smaller population size compared with other ethnic minority groups, very few centers report their incidence rates. For example, SEER data for NA is only based on the contract health service delivery area counties.

Of the few studies present in the literature, some show trends in NA that are shared by other ethnic minority groups. For example, melanomas that arise in NAs are more frequently found on sun-protected skin, although in NAs this is usually the trunk as opposed to acral or mucosal sites. In

addition, NAs also tend to present with advanced-stage disease and have decreased overall survival, following the trend of an overall lower survival rate for most cancers.[48]

Conclusions

Data show that the incidence rate of melanoma in most ethnic minority groups is increasing. The presentation and trends of melanoma among these groups is variable, reflecting their diversity. Given the relative rarity of its occurrence and unusual presentation, it is not surprising that the diagnosis of melanoma is often delayed in these populations. This delay not only results in greater rates of advanced-stage disease at presentation but also decreased overall survival. Although some studies show that the delay is likely the result of low social economic status, this is not the case for all groups. Therefore, addressing melanoma in ethnic minority populations is a complex issue. However, the medical community can engage in several endeavors that will lay the foundation for better patient care.

For example, given the evidence that preventive measures and educational efforts have dramatically impacted the diagnosis and outcome of melanoma patients, it is critical that similar efforts be directed at ethnic minority populations. Ethnic minority groups should be targeted for sun protection and skin cancer risk education. Their clinical visits should encompass full skin examinations that, at the least, include examination of sun-protected sites, such as oral and conjunctival mucosa and acral sites. Dermatologists should also emphasize regular self-skin examinations and annual visits with dentists, ophthalmologists and, if applicable, podiatrists. Dermatologists should also raise awareness with the latter group of health care providers and cosmetologists, regarding various types of melanoma presentation. With a collective effort, the detection of early stage melanoma in these rapidly expanding populations can be increased.

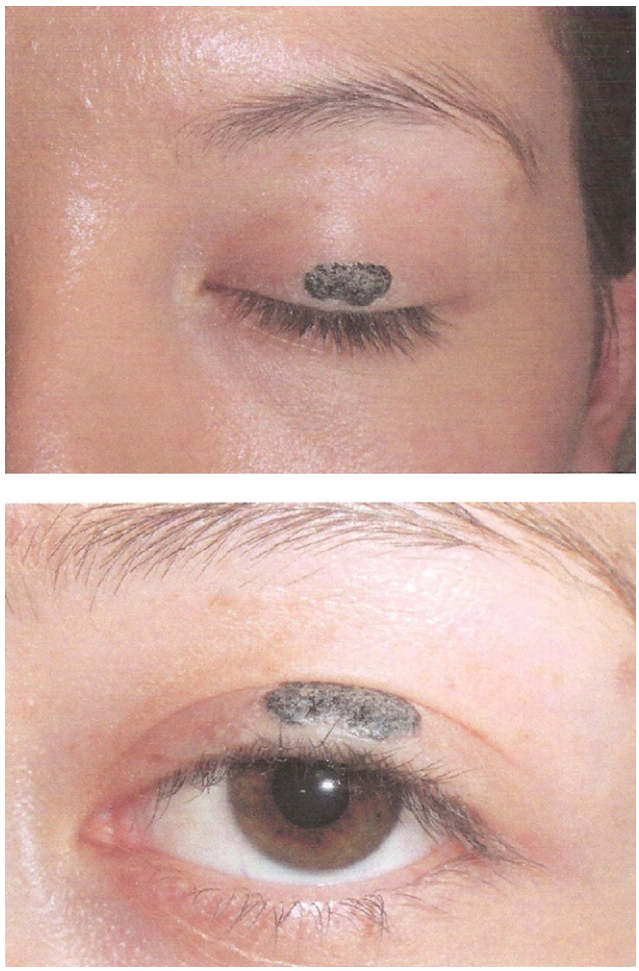

Figure 2 Melanoma primary of the upper eyelid in a Mexican-American woman.

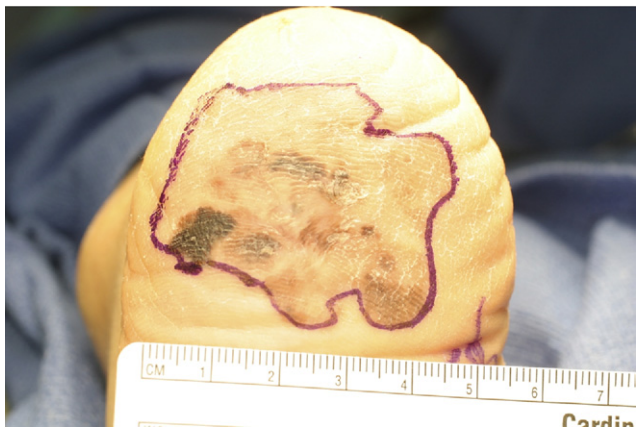

Figure 3 Acral lentiginous melanoma primary of the plantar foot in a Chinese-American male. Courtesy of Dr Stanley P. L. Leong.

One other endeavor that will aid in future patient care and research efforts is the shift to better patient descriptors. The standard repertoire of terms used to describe patients consists largely of race-based terms that have no biological basis. These labels are sometimes substituted for ethnic terms, which denote cultural groups. In addition, they are not always used consistently in scientific and epidemiologic studies. Many groups that are genetically, culturally and phenotypically different are grouped into larger "racial/ethnic" groups. For example, Arab-Americans, a group that has a relatively low incidence of melanoma, are usually categorized under Caucasian racial/ethnic groups.[49] As we continue to discover cancer-related genomic footprints that are common in specific ancestral groups, it will be important that we describe our patients by relevant scientific information, such as biogeographical ancestry. In addition, cancer registries should start to expand their repertoire of patient descriptors to include major US subpopulations.

Finally, future research efforts should be directed toward examining the etiology of melanoma in these groups. UV light is known to play a major role in the etiology of melanoma arising in people of European ancestry and is therefore relevant for certain groups that have higher levels of EA genetic admixture. In addition, some data suggest that UV light may be associated with melanoma arising in AA populations.[50] However, for the vast majority of melanoma subtypes that arise in ethnic minority populations the etiology is unknown with no established life-

style, occupational or environmental risk factors. Future investigations of skin cancer in AA, A/PA, LA, and NAs should include studies of risk factors, such as burns, trauma, diet, familial, and immunologic aspects.

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