SKIN

IN-DEPTH REVIEW

Racial and Ethnic Disparities in Malignant Melanoma: A Literature Review

Mitchell Taylor, BA[1,2], Robin Farias-Eisner, MD, PhD, MBA[1,2,3]

[1] School of Medicine, Creighton University, Omaha, NE
[2] CHI Health Creighton University Medical Center – Bergan Mercy, Omaha, NE
[3] Lynch Comprehensive Cancer Research Center, School of Medicine, Creighton University, Omaha, NE

ABSTRACT

Melanoma is a tumor arising from uncontrolled proliferation of melanocytes, neural crest derived cells responsible for production of pigment in the basal layer of the epidermis. While the prevalence of melanoma is greatest in fair-skinned populations, racial and ethnic minority populations disproportionately experience lower rates of survival when diagnosed with melanoma. Recent studies indicate that, among minority populations, melanoma tends to present at a more advanced stage with more aggressive melanoma subtypes, increased and atypical distributions over the body, and increased tumor depths. Populations of color are also thought to carry unique mutations in BRCA genes that may predispose them to developing melanoma and account for increased mortality rates. Socioeconomic status has also been linked to melanoma disparities, where limited access to quality healthcare including skin exams, surgical treatment, health insurance, and education may result in decreased melanoma survival rates. The aim of this article is to review the relationship between melanoma and underserved communities as well as discuss the current explanations behind these observations.

INTRODUCTION

Melanoma is a tumor arising from uncontrolled proliferation of melanocytes, neural crest derived cells responsible for production of pigment in the basal layer of the epidermis.[1] Although melanoma only accounts for 5% of all skin tumors, it represents the most aggressive form of skin cancer and is responsible for 75% of deaths among skin cancer patients.[2] Over the past several decades, the incidence of melanoma has grown significantly worldwide, with a faster increase than any other cancer besides lung cancer in females.[2,3] Melanoma is the seventh most common malignancy in women and the fifth most common malignancy in men worldwide.[3] In 2020 alone, 324,635 new cases of melanoma were reported worldwide accompanied by 57,043 deaths.[4] Melanoma is known for affecting younger and middle-aged individuals, with an average age of diagnosis at 57.[3] Fair skin, prolonged exposure to ultraviolet radiation, and a family history of melanoma are all documented as major risk factors for developing melanoma. As with most other forms of cancer, survival rates are significantly improved with an early diagnosis, where patients diagnosed with

stage I melanoma have a 5-year survival rate of greater than 90%.[3]

Melanoma presents with a greater variation in risk of incidence across different racial and ethnic groups compared to other forms of cancer.[2,3,5,6] Although the incidence of melanoma is greatest in fair-skinned populations, studies indicate that populations of color are reported to have lower survival rates when diagnosed with melanoma.[7] It has been established that over the past decade, a disproportionate number of deaths due to cancer in the United States have occurred in populations of color, particularly in African Americans. However, racial disparities with respect to melanoma have received little attention.[8] Potential explanations for these outcomes in minority populations include more advanced disease at presentation, more biologically aggressive tumor behavior, and socioeconomic status. Due to these uncertainties, studies have attempted to elucidate the relationship between melanoma and racial and ethnic minority groups and the causes of increased mortality. It is imperative for physicians to understand the manifestations and outcomes of melanoma in these populations as to optimize prevention, early detection, and treatment options. Therefore, the aim of this article is to review the relationship between melanoma and underserved communities as well as discuss the current explanations behind these observations.

REVIEW

Advanced Stage of Presentation

Compared to Caucasians, ethnic minority populations are more likely to be diagnosed with an advanced stage of melanoma upon clinical presentation. Studies by Cormier et. al indicate that minority populations are approximately twice as likely to present with either stage II or III melanoma compared to Caucasians.[8] Between groups, 10.2% of Hispanics, 16.7% of African Americans, 15.4% of American Indians, and 9.6% of Asian/Pacific-islanders presented with stage IV melanoma while only 3.9% of Caucasians had a similar diagnosis. African Americans presented with the greatest degree of advanced melanoma, with a fourfold increase in stage IV melanoma diagnosis compared to Caucasians. When melanoma is diagnosed at an early stage, treatment of the lesion via surgical resection is associated with favorable patient outcomes.[7] However, once melanoma has advanced to a more aggressive stage, surgical resection is less effective, and the disease becomes increasingly difficult to manage. Metastasis of melanoma has a poor long-term prognosis, where median survival with treatment ranges between 8 and 12 months.

A comparison of melanoma depth between African Americans and Caucasians indicates that African Americans on average present with deeper tumors.[9] Studies by Mahendraraj et. al showed deeper melanoma lesions in African Americans compared to Caucasians across major melanoma subtypes, including Superficial Spreading (1.26 vs. 0.83mm), Nodular Melanoma (3.50 vs. 2.93mm), and Lentigo Maligna (1.07 vs. 0.63mm), respectively. Overall, 8.1% of all African Americans diagnosed with Superficial Spreading melanoma presented with tumors deeper than 3.00mm compared to only 3.1% of Caucasians.

Additionally, racial and ethnic minority groups are also shown to have broader distributions of melanoma as well as lymph node involvement, conferring a more advanced staging and poorer prognosis.

According to Hu et. al, 26% of African Americans and 18% of Hispanics presented with regional or distant disease, compared to only 12% in Caucasians.[10] While Caucasians most commonly present with melanoma on the trunk (34.5%), African Americans frequently present with melanoma on the lower extremities and feet (56.1%).[9,11] According to Hsueh et. al, the prognosis for patients diagnosed with melanoma of the lower extremity is affected by the distance of the lesion from the trunk, where a more distal tumor carries a poorer prognosis.[12] Regarding lymph node invasion, 21.8% African Americans diagnosed with Nodular melanoma had lymph node positivity compared to only 17.8% of Caucasians. Collectively, adversative tumor characteristics burden minority populations with an advanced stage of melanoma diagnosis and overall decreased patient outcomes.

Melanoma Subtype

The presentation of melanoma among minority populations compared to Caucasians differs considerably regarding melanoma subtype. Studies show that the most common form of melanoma in African Americans is Acral Lentiginous melanoma, accounting for 36% of all melanomas in this population.[8,13] Acral Lentiginous melanoma also presents as a major subtype in other minority groups, accounting for 18% of melanomas in Asian/Pacific islanders and 9% in Hispanic whites. In contrast, Caucasians are most frequently diagnosed with the Superficial Spreading form of melanoma, while Acral Lentiginous melanoma only accounts for 1% of all Caucasian melanoma diagnoses.[9]

Acral Lentiginous melanoma has a more aggressive behavior and poorer prognosis as compared to other melanoma subtypes.[14] Acral Lentiginous melanoma presents atypically and is commonly found on the soles of the feet, palms, and nail beds.[13] As a result, it is more difficult to detect and diagnose in populations of color, often going unnoticed or misdiagnosed as a wart, fungus, or dark nail.[15] The presentation of these tumors reportedly delays diagnosis and treatment, leading to poorer patient outcomes and survival rates. Acral Lentiginous melanoma is associated with lower 5-year and 10-year survival rates compared to other melanoma subtypes; while all other cutaneous melanoma subtypes collectively have a 5-year and 10-year survival rate of 91.3% and 87.5%, respectively, Acral Lentiginous melanoma has a 5-year and 10-year survival rate of 80.3% and 67.5%, respectively.[9] Acral Lentiginous melanoma is consequently associated with a 12-fold increase in development of stage IV melanoma and a 2-fold increase in mortality.

Molecular Studies of BRCA1 and BRCA2

To better understand melanoma disparities in minority populations, studies have begun focusing on profiling genetic mutations involved with melanoma development. Historically, studies with melanoma patients have directed attention to genetic mutations in BRAF, NRAS, and KIT genes, which have long been associated with melanoma and are thought to be mutually excluding.[16] More recently, research has focused on further characterizing the role of BRCA1/BRCA2 mutations in the development of melanoma. BRCA1 and BRCA2 belong to a class of tumor suppressing genes located on chromosomes 17 and 13, respectively.[17] Together, BRCA1 and BRCA2 respond to double-stranded DNA breaks and play a critical role in DNA repair mechanisms. Cells lacking functional BRCA1/BRCA2 genes are unable to repair double-stranded DNA

breaks, allowing these cells to accumulate genetic mutations and develop into cell clones with malignant potential. The status and clinical significance of these mutations in ethnic and racial minorities have been less researched and warrant further characterization. Understanding the genetic mutations in these populations is essential for comprehensive healthcare management as well as detecting melanoma at earlier stages.

While BRCA1 mutations have been overall less associated with melanoma development, individuals with BRCA2 mutations have demonstrated an increased risk of melanoma in several reports.[18] In one study conducted by the National Cancer Institute, 3,728 individuals from breast-ovarian cancer families were evaluated, and individuals with a BRCA2 mutation were 2.5 times more likely to develop melanoma compared to those without the mutation.[19] Additional studies have established the presence of BRCA1/2 mutations in patients with a history of melanoma. In a study conducted by Debinak et. al, 630 patients with a history of melanoma and 3,700 controls were genotyped for the prevalence of three common variants of BRCA2 mutations (T1915M, N991D, and N372H).[20] This study found that the prevalence of the BRCA2-N991D variant was significantly greater in melanoma patients compared to the controls. However, association between the two other BRCA2 variants and melanoma was not proven to be statistically significant. Further research is necessary in order to determine the contribution of BRCA2 mutations in melanoma development.

Across racial and ethnic groups, there are differences in the spectrum of BRCA1 and BRCA2 mutations that may account for observed melanoma disparities.[21] In a study conducted by Golan et. al with metastatic pancreatic cancer patients, a higher prevalence of germline BRCA mutations was observed in African Americans compared to Caucasians and patients of other races.[22] African Americans also demonstrated the highest degree of BRCA2 mutations (7.1%) compared to Caucasians (4.4%), Asians (4.1%), and other groups (1.6%). However, it is important to note that only 1.3% of the screened population in this study was African American, which may limit the ability to draw definitive conclusions. Another study done by Haffty et. al found that the relative distribution of BRCA1 and BRCA2 mutations differed between Caucasian and African American breast cancer patients.[23] They found that 80% of African American patients carried mutations in the BRCA2 gene while 69% of the fair-skinned cohort harbored mutations in the BRCA1 gene. Furthermore, 46% of the African American patients had variants of unknown significance compared to only 12% in the Caucasian population. A third study conducted by Gao et. al reported similar results with African American breast cancer patients demonstrating disproportionally greater frequencies of BRCA2 mutations.[24] Their study identified that, in African Americans, four of five deleterious mutations and four of six missense mutations were involved on the BRCA2 gene. Collectively, these results indicate significant differences in BRCA1/2 mutation frequencies that may be contributing to disparities in melanoma across populations.

Socioeconomic and Demographic Factors

In addition to a more aggressive tumor biology and difficulty in diagnosing acral subtypes of melanoma, factors including socioeconomic status and access to healthcare have also been implicated in

lower melanoma survival rates in minority groups. Populations of color diagnosed with melanoma are observed to have a lower socioeconomic status; a study by Tripathi et. al demonstrated that, in a sample of patients diagnosed with cutaneous melanoma, African Americans maintained a median household income of less than $38,000 compared to $63,000 or greater in non-Hispanic whites.[25] Notably, a lower socioeconomic status has been associated with reduced 5-year survival in melanoma patients, where Chang et. al reported a decreased survival rate in both early (83.2% vs. 90.9%) and late-stage (30.0% vs. 45.5%) melanoma patients with a low socioeconomic status compared with a higher economic status.[26] A separate study conducted by Linos et. al evaluated 29,792 melanoma cases in the state of California and found that the lowest socioeconomic status groups experienced the greatest incidence of thick melanomas greater than 4mm.[27]

Access to health insurance has also been shown to vary by race and consequently affect clinical outcomes in melanoma patients.[28] Artiga et. al highlight that, during the year of 2019, 11% of African Americans, 20% of Hispanics, 22% of American Indians and Alaska Natives (AIAN), and 13% of Native Hawaiians and Other Pacific Islanders (NHOPI) were uninsured compared to only 8% of Caucasians. Of those minority patients with insurance, 37% of African Americans, 32% of Hispanics, 38% of AIAN, and 30% of NHOPI relied on Medicaid coverage while 74% of Caucasians were covered by private insurance. The type of insurance, specifically Medicaid, has been associated with provider discrimination and is thought to contribute to melanoma-related disparities in underserved populations.[29] Medicaid patients on average experience lower acceptance rates for dermatology appointments, where only 32% of Medicaid patients receive appointments while 85% of Medicare and 87% of private insurance patients are accepted for appointments. Medicaid patients also experience longer wait times for appointments; these patients wait an average of 50 days for an appointment while Medicare and private insurance patients only wait 37 days before being seen by a dermatologist.[30]

With the observed barriers to accessing healthcare, minority patients are less likely to receive the medical interventions necessary to manage skin cancers and are consequently at higher risk of developing advanced-stage melanomas. Thorough full-body skin exams performed by medical professionals are standard and critical for early detection of skin cancers like melanoma. However, studies have indicated that minorities are less likely to have received full-body skin examinations as compared to the white population. According to the National Health Interview Survey, individuals of Hispanic and African American descent are less likely to have been screened for skin cancer compared to Caucasians.[31] Their survey found that, in 2000, only 3.7% of Hispanic persons and 6.2% of black individuals received a recent skin examination as compared to 8.9% of Caucasians.

For minority patients that receive skin checks and are diagnosed with melanoma, studies indicate that these patients experience an increased period between the diagnostic biopsy and surgical excision, known as the surgical interval.[25] It is well documented that delay in treatment following biopsy is associated with increased melanoma-specific mortality rates, although surgical interval guidelines for melanoma are not well-defined.[32] Tripathi et. al found

that, when sociodemographic characteristics were controlled for, the average surgical interval for African American patients was 23.4 days while Caucasian patients only waited 11.7 days between diagnosis and surgery.[25] Furthermore, African American patients had twice the odds of experiencing surgical intervals between 41 and 60 days, three times the odds of 61 to 90 days, and five times the odds of over 90 days from the time of diagnosis to treatment.

The advanced stage of melanoma in minority populations is also thought to be due to lower skin cancer awareness in these groups. Historically, darker-skinned individuals have perceived themselves to have a reduced or no risk for developing melanoma due to increased levels of protective pigment in their skin.[33] This can also be attributed to the marketing of melanoma risks and preventions to target populations primarily consisting of blonde or red-haired and blue-eyed individuals.[27] Byrd et. al have commented on the matter, claiming that the lack of public education involving melanoma in populations of color may be a significant driver of advanced melanoma stages in these groups.[34] In a study conducted by Pipitone et. al, skin cancer awareness was compared between Hispanic and non-Hispanic Caucasians.[35] Results indicated that awareness of melanoma skin cancer and risk perception among Hispanic persons was significantly less compared to non-Hispanic Caucasians. Furthermore, in another study conducted by Buster et. al, African Americans and Hispanics were less likely to believe that skin cancer is affected by lifestyle choices, despite known impacts of ultraviolet radiation on skin cancer development.[36] Their study also revealed that these groups were more likely to believe that skin cancer is preceded by pain or other non-specific symptoms and that nothing can be done to protect against these tumors. Overall, the lower socioeconomic status associated with a number of minority populations limits access to critical healthcare and educational recourses, ultimately contributing to the observed disparities and a reduced overall awareness.

CONCLUSION

In conclusion, the number of reported melanoma cases has continued to rise in the past few decades. While the Caucasian population accounts for the highest incidence of melanoma diagnoses, racial and ethnic minority populations disproportionately experience lower rates of survival when diagnosed with melanoma. Among minority populations, melanoma tends to present at a more advanced stage with more aggressive melanoma subtypes, increased and atypical distributions over the body, and increased tumor depths. Recent studies indicate that populations of color carry unique mutations in the BRCA genes that may predispose them to developing melanoma and account for increased mortality rates. Socioeconomic status has also been linked to melanoma disparities, where limited access to quality healthcare including skin exams, insurance, and education may result in decreased melanoma survival rates. Overall, it is imperative to incorporate melanoma disparities education into physician training in order to combat the systemic issues observed and improve the poor melanoma prognosis associated with populations of color.

Conflict of Interest Disclosures: None

Funding: None

Corresponding Author:
Mitchell Taylor, BA
3920 Dewey Ave

Omaha, NE 68105
Phone: 612-356-0360
Email: mat96996@creighton.edu

References:

1. Domingues B, Lopes JM, Soares P, Pópulo H. Melanoma treatment in review. ImmunoTargets and therapy. 2018; 7:35-49.
2. Ward-Peterson M, Acuña JM, Alkhalifah MK, et al. Association between race/ethnicity and survival of melanoma patients in the united states over 3 decades: A secondary analysis of SEER data. Medicine (Baltimore). 2016; 95:e3315.
3. Heistein JB, Acharya U. Malignant Melanoma. In: StatPearls. Treasure Island (FL): StatPearls Publishing LLC, 2021:.
4. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2021; 71:209-249.
5. Leonardi GC, Falzone L, Salemi R, et al. Cutaneous melanoma: From pathogenesis to therapy. International journal of oncology. 2018; 52:1071-1080.
6. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer. 2015; 136:E359-E386.
7. Matthews NH, Li WQ, Qureshi AA, Weinstock MA, Cho E. Epidemiology of Melanoma. In: Ward WH, Farma JM (eds). Cutaneous Melanoma: Etiology and Therapy. Brisbane (AU): 2017:.
8. Cormier JN, Xing Y, Ding M, et al. Ethnic differences among patients with cutaneous melanoma. Archives of internal medicine (1960). 2006; 166:1907-1914.
9. Mahendraraj K, Sidhu K, Lau CSM, McRoy GJ, Chamberlain RS, Smith FO. Malignant melanoma in african-americans: A population-based clinical outcomes study involving 1106 african-american patients from the surveillance, epidemiology, and end result (SEER) database (1988-2011). Medicine (Baltimore). 2017; 96:e6258.
10. Hu S, Parmet Y, Allen G, et al. Disparity in melanoma: A trend analysis of melanoma incidence and stage at diagnosis among whites, hispanics, and blacks in florida. Archives of dermatology (1960). 2009; 145:1369-1374.
11. Erdei E, Torres SM. A new understanding in the epidemiology of melanoma. Expert review of anticancer therapy. 2010; 10:1811-1823.
12. Hsueh EC, Lucci A, Qi K, Morton DL. Survival of patients with melanoma of the lower extremity decreases with distance from the trunk. Cancer. 1999; 85:383-388.
13. Tas F, Erturk K. Acral lentiginous melanoma is associated with certain poor prognostic histopathological factors but may not be correlated with nodal involvement, recurrence, and a worse survival. Pathobiology (Basel). 2018; 85:227-231.
14. Alcarraz CE, Morante Z, Mas L, et al. Outcomes and prognostic factors for acral lentiginous melanoma in peruvian patients. Journal of clinical oncology. 2016; 34:e21061.
15. Gupta AK, Bharadwaj M, Mehrotra R. Skin cancer concerns in people of color: Risk factors and prevention. Asian Pacific journal of cancer prevention : APJCP. 2016; 17:5257-5264.
16. Gutiérrez-Castañeda LD, Nova JA, Tovar-Parra JD. Frequency of mutations in BRAF, NRAS, and KIT in different populations and histological subtypes of melanoma: A systemic review. Melanoma research. 2020; 30:62-70.
17. Venkitaraman AR. Cancer Susceptibility and the Functions of BRCA1 and BRCA2. Cell. 2002; 108:171-182.
18. Gumaste PV, Penn LA, Cymerman RM, Kirchhoff T, Polsky D, McLellan B. Skin cancer risk in BRCA1/2 mutation carriers. British journal of dermatology (1951). 2015; 172:1498-1506.
19. Breast Cancer Linkage Consortium, T. Cancer risks in BRCA2 mutation carriers. JNCI : Journal of the National Cancer Institute. 1999; 91:1310-1316.
20. Dębniak T, Scott RJ, Górski B, et al. Common variants of DNA repair genes and malignant melanoma. European journal of cancer (1990). 2007; 44:110-114.
21. Kurian AW. BRCA1 and BRCA2 mutations across race and ethnicity: Distribution and clinical implications. Current opinion in obstetrics & gynecology. 2010; 22:72-78.
22. Golan T, Kindler HL, Park JO, et al. Geographic and ethnic heterogeneity of germline BRCA1 or BRCA2 mutation prevalence among patients with metastatic pancreatic cancer screened for entry into the POLO trial. Journal of clinical oncology. 2020; 38:1442-1454.
23. Haffty BG, Silber A, Matloff E, Chung J, Lannin D. Racial differences in the incidence of BRCA1 and BRCA2 mutations in a cohort of early onset breast cancer patients: African american

compared to white women. Journal of medical genetics. 2006; 43:133-137.
24. Qing G, Tomlinson G, Das S, Cummings S. Prevalence of BRCA1 and BRCA2 mutations among clinic-based african american families with breast cancer. 2000; .
25. Tripathi R, Archibald LK, Mazmudar RS, et al. Racial differences in time to treatment for melanoma. Journal of the American Academy of Dermatology. 2020; 83:854-859.
26. Chang AE, Karnell LH, Menck HR. The national cancer data base report on cutaneous and noncutaneous melanoma. Cancer. 1998; 83:1664-1678.
27. Linos E, Swetter SM, Cockburn MG, Colditz GA, Clarke CA. Increasing burden of melanoma in the united states. Journal of investigative dermatology. 2009; 129:1666-1674.
28. Artiga S, Hill L, Orgera K, Damico A. Health Coverage by Race and Ethnicity, 2010-2019 <https://www.kff.org/racial-equity-and-health-policy/issue-brief/health-coverage-by-race-and-ethnicity/>. Accessed June 12,. 2021.
29. Kooistra L, Chiang K, Dawes S, Gittleman H, Barnholtz-Sloan J, Bordeaux J. Racial disparities and insurance status: An epidemiological analysis of ohio melanoma patients. Journal of the American Academy of Dermatology. 2018; 78:998-1000.
30. Resneck J, Pletcher MJ, Lozano N. Medicare, medicaid, and access to dermatologists: The effect of patient insurance on appointment access and wait times. Journal of the American Academy of Dermatology. 2004; 50:85-92.
31. Saraiya M, Hall HI, Thompson T, et al. Skin cancer screening among U.S. adults from 1992, 1998, and 2000 national health interview surveys. Preventive medicine. 2004; 39:308-314.
32. Huff LS, Chang CA, Thomas JF, et al. Defining an acceptable period of time from melanoma biopsy to excision. Dermatology Reports. 2012; 4:e2.
33. Goldenberg A, Vujic I, Sanlorenzo M, Ortiz-Urda S. Melanoma risk perception and prevention behavior among african-americans: The minority melanoma paradox. Clinical, cosmetic and investigational dermatology. 2015; 8:423-429.
34. Byrd KM, Wilson DC, Hoyler SS, Peck GL. Advanced presentation of melanoma in african americans. Journal of the American Academy of Dermatology. 2004; 50:21-24.
35. Pipitone M, Robinson JK, Camara C, Chittineni B, Fisher SG. Skin cancer awareness in suburban employees: A hispanic perspective. Journal of the American Academy of Dermatology. 2002; 47:118-123.
36. Ezenwa E, Buster K. Health Disparities and Skin Cancer in People of Color. Practical Dermatology. 2019; :38-42.