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Un-Fair Skin: racial disparities in acral melanoma research

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Abstract

Patients of colour predominately present with acral lentiginous melanoma (ALM), the most lethal subtype of cutaneous melanoma. We here advocate for increased mechanistic studies using models derived from the patient communities suffering most from ALM to develop therapies that benefit patients across all ethnic and racial groups.

Recent therapeutic breakthroughs, including targeted BRAF inhibitors and immune checkpoint blockade (ICB), for metastatic melanoma have asymmetrically benefited patients across ethnic and racial groups. Racial disparities in melanoma persist and are worsening with time for patients of colour (that is, Hispanic-, African- and Asian-descent) relative to non-Hispanic whites (NHWs)[1].

A 2021 analysis of the Surveillance, Epidemiology, and End Results (SEER) registry for US patients assessed changes in melanoma-specific survival (MSS) between the <2000 time period (when surgery, chemotherapy and interleukin-2 (IL-2) were standard-of-care) and the ≥2010 time period when modern targeted therapies and immunotherapies entered the clinical space[2]. Although MSS improved from the <2000 period to the ≥2010 period for most racial groups (except for Hispanics and non-Hispanic American Indian or Alaska Natives, which stayed the same), the greatest increase in MSS was experienced by NHWs[2]. Furthermore, there has been exacerbating disparity in MSS for patients with localized disease across all minority races compared with NHWs from <2000 to ≥2010. Specifically in Hispanic patients with regional or distant disease, disparity in MSS has worsened from the <2000 period to the ≥2010 period[2].

It is plausible that the variation in melanoma subtype distribution across ethnic and racial groups in the USA and internationally has contributed to these disparities. Acral lentiginous melanoma (ALM), a subtype of cutaneous melanoma, which frequently arises on UV-protected areas of the body (for example, palms and soles of the feet) exposed to mechanical stress comprises <3% of melanomas in NHWs and >50% of melanomas in non-white individuals (that is, African-, Hispanic-, and Asian-descent in the USA)[3-5]. Patients with ALM suffer worse 10-year MSS rates relative to patients with other forms

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Competing interests

The authors declare no competing interests.

of cutaneous melanoma (67.6% versus 87.5%)[2,3], and BRAF inhibitors are not suitable for most patients with ALM owing to their tumours having a lower frequency of *BRAF* mutations (<20% versus >50% in other forms of cutaneous melanoma)[6]. The efficacy of approved ICB strategies also appears to be reduced against ALM, potentially owing to a decreased mutational burden[6,7]. As ALM is the deadliest cutaneous melanoma subtype and only accounts for a fraction of melanomas in NHWs versus patients of colour, one could deduce this alone may explain the lower MSS rates among communities of colour. However, stratifying the ALM patient population by race and ethnicity reveals racial disparities also exist, with ALM patients of colour suffering worse outcomes relative to NHW patients[4,5]. In addition, ALM racial disparities have continued to worsen for Hispanic and non-Hispanic Blacks (NHBs) relative to NHWs from the <2000 period to the ≥2010 period[2].

Despite comprising <3% of melanomas in NHWs, nearly all existing ALM models and genomic sequencing efforts have originated from NHW patient tumours, making the translatability of findings stemming from these homogeneous sources to populations of colour unclear. To date, published ALM cell line-based pre-clinical research to define functional drivers of ALM progression and therapy resistance that may inspire clinical trials to improve the outcome of patients with ALM remains inadequate, and even more scarce are publications using ALM models derived from communities of colour.

Although addressing cancer disparities for patients of colour with ALM (and indeed all melanoma subtypes) represents one of the greatest challenges of the field, there are viable solutions to this issue, some of which we propose here.

- Public health campaigns could be launched to spread awareness of ALM among communities of colour to increase the chances for patients to catch their melanomas early. Minority populations currently present at more advanced stages than NHWs, which may contribute to survival disparities[2]. The ‘ABCDEs’ (Area, Border, Colour, Diameter, Evolving) public health campaign successfully raised melanoma awareness for the lay public to increase early diagnosis; however, the acronym does not apply to ALM owing to variations in presentation on plantar surfaces and the possibility of misdiagnosis for common benign conditions (for example, ingrown toenails and foot ulcers). An acronym developed for ALMs arising on the feet is ‘CUBED’, standing for Coloured lesions where any part is not skin colour, Uncertain diagnosis, Bleeding lesions on the foot or under the nail, Enlargement of a lesion or ulcer despite therapy, and Delay in healing of a lesion >2 months[8]. The CUBED system should be spread to all communities throughout the world and to health professionals (for example, podiatrists) and industries (for example, foot massage parlours and nail salons) that focus on feet.
- Underrepresentation in clinical trials should be reversed to increase knowledge of whether therapies can benefit the entire population. Approximately 35.7% of the US population is Black or African American, Hispanic or Asian, yet historic melanoma clinical trials included ≤5% of patients of Hispanic-, African- or Asian-descent. For example, in the BRIM-3 (NCT01006980) clinical trial, which led to the approval of the BRAF inhibitor vemurafenib, 671 out of 672 (99.9%)

patients were of white race, and in the CheckMate067 (NCT01844505) clinical trial, which led to the approval of the combination of the immunotherapies nivolumab plus ipilimumab, 921 out of 945 (97.5%) patients were of white race with only 10 Asian people, one American Indian or Alaska Native, and one Native Hawaiian or other Pacific Islander enrolled.

- Representation in preclinical research should be increased. Preclinical research provides rationale for clinical trials, and diverse repositories of melanoma models are needed to ensure trials with the greatest potential to benefit all patient populations are launched. Recently, the Melanoma Research Alliance excellently catalogued ALM models available for sharing with the research community from laboratories around the globe. Despite this great step forward, most are derived from NHWs with only two out of the 25 ALM models derived from Hispanic patients.
- Grant funding bodies should request information regarding how an applicant's proposed studies address race and ethnicity as a biological variable.
- Documentation and transparency in manuscripts and oral presentations at symposia of the race and ethnicity landscape of the tumour models utilized should be standardized to promote awareness of the applicability of the results to the general population.
- Care across ethnic and racial groups should be standardized. African Americans, along with patients with lower incomes, are less likely to be administered immunotherapy relative to white people or patients with higher incomes (>US $63,000)[9]. This may be addressed using expanded-access programmes for providing expensive therapies (for example, targeted therapies and ICB) to underserved communities, as well as developing countries. One example towards this end was an expanded-access programme in South Africa to evaluate the efficacy of the cytotoxic T lymphocyte-associated antigen 4 (CTLA4) antibody, ipilimumab, in an African patient population[10]. However, only two of the 108 patients in this trial were Black (1.85%), while 93 of the 108 were white (86.1%). Although melanoma incidence in the white and Black populations of South Africa is 23.2 and 0.5 per 100,000 individuals, respectively, the demographic makeup of South Africa being predominantly Black people (80.2% Black, 8.4% white) brings an estimated 238 new cases (~17% of new cases) in Black individuals and 1,156 new cases in white individuals every year in South Africa.

In summary, we advocate for increased basic biology, translational and clinical studies of ALM (and all melanoma subtypes) across diverse patient populations to increase the potential to mitigate racial disparities and increase the curative potential of therapy for every patient. Although racial disparities in melanoma (and numerous other cancers and diseases) are caused by complex and multifactorial factors (some not touched upon here), we believe addressing them as a united international community will be vital towards achieving our goal to provide equal therapeutic benefit to patients of all racial and ethnic backgrounds.

Appendix

RELATED LINKS

ALM models: https://www.curemelanoma.org/blog/article/mras-acral-melanoma-cell-line-catalog-a-launching-pad-for-research

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