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Income-associated discrepancies in melanoma survival

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ABSTRACT

The Surveillance, Epidemiology, and End Results (SEER 18) database is the largest national registry for cancer-related patient data in the United States. Black populations consistently have shown poorer survival statistics, possibly due to later stages of presentation, increased tumor aggressiveness, treatment noncompliance, or other debated causes. Our goal in this study is to look at a socioeconomic marker that may link all of these causes, namely median income level, and derive the extent of influence a patient's financial resources can have on overall survival. Original cases from the aforementioned database were identified, with unknown racial status cases excluded from the final dataset. Survival data by geographical county was collected from the SEER database and correlated to US Census Bureau median income data to uncover meaningful statistical relationships. Blacks were noted to present at later ages (60+years), with deeper invasive lesions (median 1.255 mm vs 0.60 mm), and higher rates of ulceration (35.9% vs 13.0%) than White patients. Whites were found to overall fare better than Blacks for all time intervals (Year 1–5) following diagnosis, based on mean survival data ($p < 0.05$). Blacks have higher survival rates for the same time intervals (Year 1 to Year 5) when survival statistics adjusted for income ($p < 0.05$). Significant correlations were seen between presentation parameters, income, and overall survival. These findings identify a major socioeconomic issue to address within the policy-making framework and endorse earlier intervention for underprivileged populations.

1. Introduction

With nearly 76,100 invasive cases diagnosed in the United States in 2014, melanoma is the fifth and seventh most common cancer in men and women, respectively [1]. The cancer chiefly arises from malignant transformation of melanocytes, a process consisting of benign precursor lesion formation (melanocytic nevus), followed by development of a dysplastic nevus, progressing through radial and vertical growth phases of the primary lesion, and ultimately metastasis. Genetic and epigenetic mutations are thought to drive progression through these steps [2,3]. Though well-studied, many patients have disease progression that may deviate from this typical model and may be more complex in nature when considering melanoma risk factors such as family history, fair skin, immunosuppression, and UV radiation (UVR). Melanoma causation and risk association is complex, with genetic and environmental factors affecting an individual's risk. Caucasian race, male sex, and older age are well-known factors associated with an increased risk of developing melanoma [3–6]. Surgical approach is considered the mainstay of care in the management of melanoma for diagnostic, therapeutic, or palliative purposes [7]. Additionally, invasion depth, mitotic rate, and clinical morphology are deemed to be powerful prognostic factors. The survival rate of stage IV metastatic melanoma disease is generally very poor, with a median survival of 6–9 months and a 5-year survival of 5–10%. 10-year survival rate of $< 50\%$ has been observed in patients with stage IIb, IIc and III melanomas [8–11].

Personalized treatment options for advanced melanoma have grown tremendously in recent decades, with emerging alternatives to the “impersonalized” cytotoxic chemotherapy (dacarbazine, temozolomide with vinblastine and cisplatin) and cytokine-based therapy (IL-2 and interferon-alpha), that at one time represented mainstay strategy in the treatment of locally advanced or metastatic melanoma [12–15]. Personalized therapy that aims to target certain mutations on a per-patient basis, have also gained considerable momentum. Molecular targeted therapy demonstrated significant efficacy as well, with Vemurafenib and Dabrafenib, both BRAF inhibitors, showing rapid initial disease stabilization. However their efficacy is restricted to patients with BRAFV600-mutant melanomas and drug resistance develops

Abbreviations: UVR, Ultraviolet Radiation; SEER, Surveillance, Epidemiology, and End Results; NCI, National Cancer Institute; ICD-O, International Classification of Diseases for Oncology; SSE, Self-Skin Exam

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leading to disease progression, with median progression-free survival limited to 5–7 months [16–19].

The field of immunotherapy and targeted drug delivery has seen remarkable achievements over the past decade alone. Checkpoint inhibitors have shown wide success in treating melanoma. Ipilimumab, a humanized anti-CTLA-4 monoclonal antibody, was one of the first successes in prolonging survival of patients with advanced melanoma [20]. PD-1 and PDL-1 antibody, also checkpoint inhibitors, showed durable responses and curative outcomes with fewer autoimmune toxicities and adverse effects [21]. Current clinical trials at Yale and other institutions are aiming to evaluate the presumed synergistic effect with combination therapy of these two agents [22,23]. Efforts currently exist to study the effects of combining checkpoint blockades with personalized genotype-driven care with the aim of exploiting cancer susceptibilities on both immunological and genetic fronts [24]. Initial results appear promising, though challenges remain and long-term studies are necessary [25–27].

Personalized medicine extends beyond genetic sequencing and lab values, as there is an increasing understanding that epidemiology and socioeconomic considerations help develop a more holistic approach to the unique circumstance of each patient [28]. This paradigm shift in the delivery of medicine offers many opportunities for improved clinical decision-making, both before and after a cancer diagnosis, and also preserves the delicate "physician-patient" relationship by incorporating patient education and personalized preferences [29]. Due to larger incidences and case volumes in White populations, Black cases are generally considered understudied, though survival and response to treatment is observed to be lower in Blacks. Much is reported regarding race-specific incidence, stage at diagnosis, and survival for specific diseases such as melanoma, but no study has investigated the relationship between county-specific trends in income with the most recently available Surveillance, Epidemiology, and End Results (SEER) data describing survival and tumor characteristics. This study aims to not only explore the strength of such correlations but also expand the narrative on how to improve upon the delivery of care to both populations.

2. Methods

Data from the National Cancer Institute's (NCI's) SEER Program database was obtained for cases of "Melanoma of the skin", including several parameters such as age, race and sex at cancer diagnosis, observed and relative survival rates, and county of diagnosis. This filtered SEER data, particularly survival, is referenced to 2010 US population estimates. The statistics presented herein, with the exception of mortality, were obtained from data collected at population-based registries that participate in NCI's SEER Program [30]. Cancers are coded according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3). Cases collected before 2001 were machine-converted to ICD-O-3 codes. All statistical analysis and observations were accomplished using JMP Version 8 software (SAS Institute NC, USA).

3. Results

Of the 304,476 racially-stratified patients, African-Americans were noted to present at later ages at diagnosis. Forty-one percent (n=667) of Blacks presented between the ages of 60 and 79, while 37.6% of Whites (n=108,809) presented in the same age interval. Presentation over the age of 80 was seen in 15.8% (n=254) of Blacks compared to 12.6% (n=36,395) of Whites. These values are depicted in Table 1.

64.1% (n=419) of Blacks presented with non-ulcerated lesions, compared to 87.0% (n=121,585) of Whites. Ulcerated lesions were reported for 35.9% (n=235) of Blacks and only 13.0% (n=18,093) of Whites with a calculated relative risk of 2.77 (CI 95%, 2.50–3.08) All values are significant as illustrated in Table 1.

Analysis of Breslow depth indicated that 43.1% of Blacks (n=277) presenting with lesions less than or equal to 1 mm, compared to 68.3% (n=95,677) of Whites. A greater percentage of Blacks also present with lesions between 1 mm up to 2 mm in depth (17.1% (n=110) compared to 16.7% (n=23,336)). Furthermore, 18.5% of Blacks (n=119) and 8.8% (n=12,348) of Whites presented with lesions between 2mm and 4mm. Significantly more Blacks (21.1%, n=136) presented with lesions 4.01 mm and higher in depth compared to 6.2% (n=8714) with a calculated relative risk of 3.94 (CI 95%, 3.43–4.53). The mean depth for Blacks was determined to be 2.462 mm compared to 1.195 mm in Whites. The median depth is calculated to be 1.255 mm compared to 0.60 mm in White patients.

When classifying lesions according to histological subtypes, it was observed that although there were a greater number of general malignant melanoma in Whites, this subtype makes up a greater proportion of tumors in Blacks (55.91% vs. 49.84%). Cases of nodular melanoma are similar in both races, with 8.07% of blacks and 7.47% of Whites presenting with this subtype. Acral lentiginous melanoma is much more common among blacks (14.74% vs 0.80%). White patients present with a larger share of

Table 1
Demographical and clinical data of the stratified patients.

Category	Blacks (n)	Blacks (%)	Whites (n)	Whites (%)	Relative risk	[95% CI][a]
Age at diagnosis, years						
< 40	226	14.0	43,390	15.0	1.00	
40–59	464	28.8	100,960	34.9	0.96	[0.91–1.01]
60–79	667	41.4	108,809	37.6	1.04	[1.01–1.09]
80+	254	15.8	36,395	12.6	1.16	[1.07–1.26]
Ulcerated status						
Not ulcerated	419	64.1	121,585	87.0	1.00	
Ulcerated	235	35.9	18,093	13.0	2.77	[2.50–3.08]
Breslow thickness, mm						
≤ 1 mm	277	43.1	95,677	68.3	1.00	
1.01–2.00 mm	110	17.1	23,336	16.7	1.45	[1.24–1.70]
2.01–4.00 mm	119	18.5	12,348	8.8	2.63	[2.26–3.06]
4.01+ mm	136	21.2	8714	6.2	3.94	[3.43–4.53]
Mean thickness	2.462 mm		1.195 mm			
Median thickness	1.255 mm		0.60 mm			

[a] [95% CI], 95%, confidence interval.