The impact of socioeconomic status on melanoma clinical trial participation: an observational cohort study from Australia

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Summary points

The importance of recruiting a wide range of subjects to melanoma clinical trials

- In the last decade alone, evidence from major melanoma trials has changed the way diagnostic imaging, surgery, chemotherapy, radiotherapy and immunotherapy are practiced and now tailored to suit the individual.
- In order to ensure the generalizability of the results from clinical trials, a wide range of subjects needs to be recruited.
- People of low socioeconomic status (SES) have been reported to miss out on the opportunity to participate in many cancer clinical trials.

Study methods

- We performed a retrospective, single-center observational study at the Melanoma Institute Australia and assessed the factors affecting melanoma clinical trial participation using logistic regression.

Factors predicting clinical trial participation

- Clinical trial participation occurred in 2304 out of 9074 patients (25%), with surgical trials recruiting the largest number of participants (1453; 63%).
- Multivariate analyses showed a lower likelihood of trial participation with each year of increasing age (odds ratio [OR]: 0.99; 95% CI: 0.98–0.99) and males were more likely to participate than females (OR: 1.18; 95% CI: 1.07–1.30). Patients with American Joint Cancer Committee stage II or III disease at initial presentation were much more likely to participate than patients with stage I disease (OR: 2.81 [95% CI: 2.50–3.16] and OR: 4.55 [95% CI: 3.91–5.30], respectively).
- SES did not affect trial participation.

Implications for policy & practice

- The identification of 'low-participation' groups could help tailor recruitment strategies in order to ensure the representative participation of those who are affected by melanoma.
- Explanations for why men participate in melanoma trials more than women may include the exclusion criteria for women who are pregnant or planning to become pregnant, financial barriers or perceived out-of-pocket costs associated with participation or insufficient time to participate as a consequence of family care-giving responsibilities.
- The reporting of the SES of trial participants enables judgments to be made regarding the generalizability of the trial findings.

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SUMMARY Aim: This study aims to determine whether socioeconomic status (SES) is associated with participation in melanoma clinical trials. **Patients & methods:** A retrospective, single-center observational study was conducted at the Melanoma Institute Australia. Factors affecting clinical trial participation were assessed using logistic regression. **Results:** Of 9074 patients, 2304 (25%) participated in a clinical trial. Multivariate analysis indicated males compared with females (odds ratio [OR]: 1.18; 95% CI: 1.07–1.30) and patients with American Joint Cancer Committee stage II or III disease (but not stage IV disease) were more likely to participate in trials than patients with stage I disease (OR: 2.81 [95% CI: 2.50–3.16] and OR: 4.55 [95% CI: 3.91–5.30], respectively). SES did not affect trial participation. **Conclusion:** Our data suggest that SES is not a significant predictor of melanoma clinical trial participation when adjusted for other factors.

KEYWORDS

- clinical trials • equity
- melanoma • participation
- socioeconomic status

Cutaneous melanoma imposes a heavy burden of morbidity and mortality on fair-skinned populations worldwide [1–3]. The use of clinical trials in order to evaluate the efficacy of new treatments is fundamental to guiding future clinical practice and improving melanoma health outcomes. In the last decade alone, evidence from major melanoma trials has changed the way diagnostic imaging, surgery, chemotherapy, radiotherapy and immunotherapy are practiced and now tailored to suit the individual [4–7]. In order to ensure the generalizability of results from clinical trials, a wide range of subjects needs to be recruited. This includes variation in patient and disease-related characteristics, including participant age, sex, socioeconomic status (SES), geographic residence, melanoma subtype, genetic factors, comorbid conditions and sun protection behaviors [8].

People of low SES have been reported to miss out on the opportunity to participate in clinical trials [9]. This not only raises an issue of potential inequity, assuming there are benefits to be gained from trial participation regardless of intervention allocation, but also hampers the ability to generalize the results to all sectors of the community. In the past, melanoma was considered to be a disease that affected more affluent populations; however, there has recently been a rise in the incidence of melanoma in the more socially deprived areas of the UK [10] and poorer coastal towns in Australia [11]. In fact, in 2011, nine of the ten local government areas with the highest standardized incidence ratio of melanoma in New South Wales, Australia, were in areas of relative socioeconomic disadvantage [11].

Low SES has been reported to be a barrier to participation in clinical trials of other cancers due to several factors, including the costs associated with trial participation (e.g., additional specialist visits or out-of-pocket payments for diagnostic tests) [12,13], logistic barriers to attending multiple services in multiple centers, particularly for the

assessment of trial eligibility (screening) [14,15] and associated cultural or linguistic barriers [16,17]. The single study of trial participation we identified in the melanoma population (albeit ocular melanoma) found somewhat different results from those in many other cancers, whereby people of an older age (≥ 60 years), lower education level and those with nonmanagerial jobs were more likely to participate in a clinical trial than their younger, more educated counterparts [18]. The aim of the present study is therefore to determine whether SES is associated with participation in clinical trials for people with cutaneous melanoma. Our hypotheses were that low SES would be negatively associated with trials participation and that close proximity to the trial center would be positively associated with participation. Our research report follows the format of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [19].

Patients & methods

• Study design

We conducted a retrospective, single-center observational study among consecutive patients of the Melanoma Institute Australia (MIA) diagnosed with cutaneous melanoma between 1 January 1995 and 31 December 2010. Based in Sydney, Australia, the MIA is one of the largest melanoma treatment centers in the world. The center hosts a range of clinical trials for all American Joint Cancer Committee (AJCC) stages of melanoma across the disciplines of surgery, radiotherapy, chemotherapy, immunotherapy and the behavioral sciences. Data for this study were obtained from the MIA research database, in which patients have given consent for their records to be used for research studies. Data were extracted in December 2012, which allowed sufficient time for the data entry of initial treatment and outcomes for patients diagnosed in the final year of the study. The information that was

collected included demographic data, detailed clinical treatment data, diagnostic investigations data, clinical trial participation data, including trial type, follow-up consultations and relevant melanoma, and general health outcomes data.

Patients of any age with a biopsy-proven invasive cutaneous melanoma and any AJCC stage of disease at initial presentation were included. Patients referred from overseas centers who did not have an Australian residential address were excluded from the study. Follow-up after initial treatment was recorded by clinicians at the MIA and via correspondence received from other health professionals, such as the patient's primary care physician.

The primary outcome was participation in a clinical trial (yes/no) at any time during the patient's melanoma treatment or follow-up. A clinical trial was defined as an experimental research study of any phase (i.e., Phase I to Phase IV) that required written informed consent and was not a part of routine melanoma care. The clinical trial could be randomized or nonrandomized and could involve an intervention from any discipline or combination of disciplines (e.g., surgery and immunotherapy). Explanatory variables included patient characteristics, such as age at melanoma diagnosis, sex, SES, country of birth, marital status, residential address and year of diagnosis, as well as tumor characteristics, such as Breslow thickness, ulceration, histopathological subtype, tumor mitotic rate, anatomical body site, AJCC stage of disease at initial presentation, date of last follow-up and follow-up status. SES was calculated using the Index for Relative Socioeconomic Advantage and Disadvantage based on Australian residence census collection districts, which is described in detail below [20].

Three variables for SES and access to healthcare were used: the Index for Relative Socioeconomic Advantage and Disadvantage, which categorizes census collection districts (small areas of ~200 similar households) across Australia into deciles of increasing SES, known as Socioeconomic Index For Areas (SEIFA) scores; the Accessibility Remoteness Index of Australia (ARIA), which allocates a remoteness index between 1 (metropolitan cities) to 5 (very remote areas) on the basis of access to essential services; and the straight-line distance from the patient's home residence to the MIA trials center. Each of these variables was generated in a similar fashion. First, the patient's residential addresses were geocoded into latitudes

and longitudes, using the GPS Visualizer's Easy Batch geocoder [21]. Second, a specialized mapping software program (ArcGIS [22]) was used to map these coordinates to the 2006 Australian Bureau of Statistics census collection districts. Each district was assigned an individual SEIFA and ARIA score that was then attributed to each patient. Finally, the Euclidean or straight-line distances between the patients' residences and the MIA were calculated using the ArcGIS software's spatial analyst function and reported in kilometers.

• Statistical methods

Our analyses were designed to examine the relevance of SES as a predictor of melanoma clinical trial participation. Variables with missing data for more than 30% of the study sample were excluded. Patient age, the SEIFA index deciles, the ARIA index quintiles and distance in kilometers were treated as continuous variables. AJCC stage of disease at initial presentation was treated as a categorical variable, with stage I as the referent group. Following univariate analyses and the consideration of confounding factors, a backward stepwise method was used in order to construct logistic regression models, where variables that had a p-value of greater than 0.25 were excluded. Goodness of fit was tested using the Hosmer and Lemeshow χ^2 test and the results of the regression models were presented as odds ratios (ORs) for the likelihood of participating in a melanoma clinical trial. Ratios with a p-value of <0.05 were considered to be statistically significant.

Results

Between 1995 and 2010, 9074 patients with invasive melanoma were identified (mean age: 58 years; 57% males). The majority of patients (86%) were AJCC stage I or II at initial presentation, and the median Breslow tumor thickness was 1.10 mm (Table 1). The median distance between the patient's home and the MIA was 27 km (interquartile range: 12–87 km); over three-quarters of the patients lived in metropolitan cities, with the majority (82%) from areas of medium-to-high SES. Patients resided in all states of Australia, but most were from New South Wales. Three-quarters of the study cohort were diagnosed between 2004 and 2010 and the median follow-up or the whole group was 35 months (interquartile range: 13–73 months), with 915 out of 9074 patients (10%) lost to follow-up at the final recording of melanoma status.

Table 1. Sociodemographic and tumor characteristics of the study sample (n = 9074).

Factor	Patients (n)	Percentage
Age at diagnosis of primary melanoma		
Median (IQR)	58 (45–69)	–
≤30 years	685	7.5
31–50 years	2535	27.9
51–70 years	3801	41.9
>70 years	2053	22.6
Sex		
Males	5126	56.5
Females	3948	43.5
Birth country		
Australia/New Zealand	1401	15.4
Outside Australia	3933	43.3
Not documented	3740	41.2
Marital status		
Single	291	3.2
Married/ <i>de facto</i>	1264	13.9
Divorced/widowed/separated	169	1.9
Not documented	7350	81.0
Socioeconomic status		
Low (SEIFA deciles 1–3)	1601	17.6
Medium to high (SEIFA deciles 4–10)	7473	82.4
ARIA (remoteness index)		
1 (metropolitan cities)	6949	76.6
2 (inner regional)	1570	17.3
3 (outer regional)	519	5.7
4 and 5 (remote and very remote)	36	0.4
Distance between home & melanoma clinic (km)		
Median (IQR)	27.0 (12.2–86.8)	–
≤10	1855	20.4
10.1–30	2877	31.7
30.1–100	2265	25.0
100.1–400	1637	18.0
>400	440	4.8
Melanoma subtype		
Acral lentiginous	84	0.9
Desmoplastic melanoma [†]	565	6.2
Lentigo maligna melanoma	399	4.4
Superficial spreading melanoma [‡]	4220	46.5
Nodular melanoma	1613	17.8
Mixed [§]	2193	24.2
AJCC stage		
Stage I	5543	61.1
Stage II	2268	25.0
Stage III	876	9.7

[†]Desmoplastic melanoma (pure and with neurotropia).
[‡]Superficial spreading melanoma (pure, with Hutchinson's melanotic freckle and with nodular melanoma).
[§]Mixed, occult and malignant blue nevus plus histology unknown.
 AJCC: American Joint Cancer Committee; ARIA: Accessibility Remoteness Index of Australia; IQR: Interquartile range;
 SEIFA: Socioeconomic Index For Areas.

Table 1. Sociodemographic and tumor characteristics of the study sample (n = 9074) (cont.).

Factor	Patients (n)	Percentage
AJCC stage (cont.)		
Stage IV	115	1.3
Unclassified	272	3.0
Breslow thickness (mm)		
Median (IQR)	1.10 (0.60–2.20)	–
0.01–1.0	4028	44.4
1.01–4.0	3748	41.3
>4.0	900	9.9
Not documented	398	4.4
Last follow-up status		
Alive, no sign of recurrence	6473	71.3
Alive, status unknown	130	1.4
Alive, with melanoma	316	3.5
Dead, cause unknown	223	2.5
Dead, cause melanoma	896	9.9
Dead, cause not melanoma	121	1.3
Lost to follow-up	915	10.1

[†]Desmoplastic melanoma (pure and with neurotropia).
[‡]Superficial spreading melanoma (pure, with Hutchinson's melanotic freckle and with nodular melanoma).
[§]Mixed, occult and malignant blue nevus plus histology unknown.
AJCC: American Joint Cancer Committee; ARIA: Accessibility Remoteness Index of Australia; IQR: Interquartile range;
SEIFA: Socioeconomic Index For Areas.

Clinical trial participation occurred in 2304 out of 9074 patients (25%), with surgical trials recruiting the largest number of participants (1453, 63%; [Table 2](#)). Of the 2304 clinical trial participants, 1384 (60%) were male. Over 1000 AJCC stage I patients and 794 stage II patients at initial presentation were enrolled in trials over the 15-year study period.

Univariate logistic regression analyses for the cohort showed that patient age, sex, SES, remoteness index and AJCC stage of disease at initial presentation were significant predictors of clinical trial participation. Notably, people from areas of higher SES were slightly less likely to participate than people from areas of low SES. Multivariate analyses showed that increasing age was associated with a lower likelihood of trial participation (OR: 0.99; 95% CI: 0.98–0.99) and males were more likely to participate than females (OR: 1.18; 95% CI: 1.07–1.30). Patients with AJCC stage II or III disease at initial presentation were much more likely to participate than patients with stage I disease (OR: 2.81 [95% CI: 2.50–3.16] and OR: 4.55 [95% CI: 3.91–5.30], respectively; [Table 3](#)). Patients with stage IV disease were not significantly more likely to participate in trials than patients with stage I disease (OR: 1.39; 95% CI: 0.88–2.18). While there was a trend for patients from more

geographically remote areas compared with less remote areas of Australia to participate in trials, this was not statistically significant ($p = 0.07$). Distance from home to the MIA was not a significant predictor ($p = 0.06$) and SES status was no longer a significant predictor of clinical trial participation ($p = 0.78$).

Discussion

This is the largest study regarding melanoma clinical trial participation reported to date, as far as we are aware. Our data suggest that a quarter of all patients attending the MIA participate in clinical trials. We found that AJCC stage of disease at initial presentation was the strongest predictor of melanoma clinical trial participation and neither SES, remoteness nor proximity to the MIA were significant predictors when adjusted for relevant covariates. Interestingly, men were more likely to participate than women, and older people were slightly less likely to participate than younger people.

Our high rate of trial participation is very different from the findings of other cancer centers in the USA, where one in 20 patients are typically enrolled in trials [23]. In the UK, the National Cancer Research Institute has reported that, over the last decade, participation in clinical

Table 2. Clinical trial type by American Joint Cancer Committee stage of disease at initial presentation.

Clinical trial type	American Joint Cancer Committee stage of disease											
	Stage I		Stage II		Stage III		Stage IV		Stage unknown		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Chemotherapy	7	11	22	34	25	38	3	5	8	12	65	3
Follow-up of melanoma	66	85	8	10	2	3	–	–	–	–	76	3
Immunotherapy	26	27	24	25	41	42	2	2	3	3	96	4
Pathology/tumor bank	216	42	147	28	90	17	11	2	26	5	490	21
Psychosocial outcomes	38	60	14	22	9	14	–	–	1	2	62	3
Radiotherapy	12	23	16	30	20	38	4	8	1	2	53	2
Surgery	638	44	561	39	238	16	3	0	13	1	1453	63
Surgery/chemotherapy	–	–	1	25	2	50	1	25	–	–	4	<1
Unknown	–	–	1	20	3	60	1	20	–	–	5	<1
Total	1003	43	794	34	430	18	25	1	52	2	2304	100

studies has increased from one in 26 to one in six diagnosed patients [23]. In Australia, the national cancer agency (Cancer Australia) has provided substantial funding in order to increase cancer trial participation rates, with a specific focus on culturally and linguistically diverse groups and those from rural or remote areas [24]. The high rate of recruitment at the MIA may be due to a relatively healthy patient population, who are predominantly English speakers, which makes discussions of trials and the process of informed consent relatively straightforward. It may also be due to a ‘trials culture’ within the MIA, along with the necessary personnel and expertise to accommodate clinical research. It was no surprise that AJCC stage of disease was a significant predictor of trial participation, as the majority of adjuvant intervention trials target patients who are at high risk of recurrence. However, the MIA does offer many other noninterventional trials that investigate, for example, histopathological tumor response and psychosocial outcomes, and these studies are not restricted to a particular AJCC stage of disease. Overall, our findings are similar to those reported in the COMS ocular melanoma study [18], in that low SES was not a barrier to clinical trial participation.

• Limitations

Our data set was restricted to routinely collected data from clinical practice and, consequently, we did not have complete information on individual-level measures of SES, such as the patient’s highest education level achieved, patient income level or occupational group. Instead, we relied on a government index of area-level SES, which

classifies small areas based on a comprehensive number of household socioeconomic indicators, such as number of bedrooms, equivalized household income, proportion of people in professional or managerial occupations, proportion of adults who have attended university, marital status, car ownership and broadband internet access. One potential issue with the use of this variable is the misclassification of individuals. For example, people of relative social advantage who choose to reside in an area of disadvantage may be classified as being of low SES. Our strategy to minimize misclassification was to use the smallest area for SES – the census collection district with approximately 200 households – rather than the larger area of postal code, which can include up to 4000 households. As an aside, the census collection district boundaries in Australia changed between 2001 and 2006 [20], resulting in a few residential addresses changing districts and therefore SES levels, but these few cases did not have a significant effect on the results.

Our study included patients treated at a single center in Australia (the MIA), which has a substantial clinical trials infrastructure and acts as a tertiary referral center. Some patients in this cohort may have been specifically referred to the MIA for consideration of a clinical trial. It is therefore likely that the high trial participation rate and the distance travelled by patients to attend the center may only be generalizable to other specialist melanoma treatment centers with a similar infrastructure and referral process. However, the factors affecting trial participation (severity of disease, age and sex) are likely to be similar in centers elsewhere. A further limitation

was the unknown follow-up status of 10% of our cohort that could be improved with linkage to the National Death Index or state cancer registry.

• Interpretation

Our findings contain important messages for melanoma clinicians and research staff. First, when screening potential clinical trial candidates and discussing trial eligibility, it is important to consider people of all socioeconomic backgrounds, as well as those who live some distance from the trials center, as they may see great value in participation and be willing to be enrolled in an experimental protocol, even if it requires frequent visits to the center. Second, we must consider that upper age limits may exclude older people who may otherwise have adequate performance status and are willing to be involved [25]. As the median age of patients with melanoma is steadily increasing, it is becoming more important to ensure that new treatments are fully evaluated in the older population. Third, we must ensure that clinical trials for all stages of melanoma, including stage IV disease, are open and available for patients. This may require the referral of patients to colleagues at other melanoma treatment centers, as it may not be efficient to have all trials open at all sites. In Australia, web-based initiatives hosted by the Australia and New Zealand Clinical Trials Registry, Cancer Australia [26] and the Cancer Council NSW provide a useful list of trials by center, including those that are open to recruitment, and these initiatives are accessible to the clinician or the lay person.

• Implications for policy

Participation in clinical trials has been reported to improve patient outcomes in chronic diseases other than cancer, regardless of whether the patient receives a new drug or treatment [27]. For cancer patients, the evidence is less clear [28]; however, all patients should be informed about trials for which they may be eligible and given the opportunity to participate in them, as there is little doubt that trials improve the treatment of future patients. The identification of ‘low-participation’ groups can help tailor recruitment strategies in order to ensure the representative participation of those who are affected by melanoma. We encourage the reporting of the SES of trial participants in order to enable judgments to be made regarding the generalizability of the trial findings.

Further research is needed in order to investigate why women were significantly less likely to participate in trials than men, even when adjusted for disease severity. One explanation may be the exclusion criteria for women who are pregnant or planning to become pregnant. Other explanations may include financial barriers or perceived out-of-pocket costs associated with participation or, alternatively, insufficient time to participate as a consequence of family care-giving responsibilities. Future studies should assess clinical trial participation for all melanoma patients on a population (i.e., statewide or national) basis.

Conclusion

Our data show that a very large proportion of patients attending the MIA participate in

Table 3. Multivariate logistic regression for factors predicting clinical trial participation in patients with invasive melanoma (n = 9,074)

Factor	Odds ratio	95% CI		p-value
		Lower	Upper	
Age at primary diagnosis (per year increase)	0.99	0.98	0.99	<0.01
Sex (males vs females)	1.18	1.07	1.30	<0.01
Socioeconomic status (per decile increase)	1.00	0.98	1.02	0.78
ARIA (per quintile increase)	1.10	0.99	1.22	0.07
Distance (per km increase)	1.00	1.00	1.00	0.06
AJCC stage (referent group: stage I): overall	–	–	–	<0.01
AJCC stage II (referent group: stage I)	2.81	2.50	3.16	–
AJCC stage III (referent group: stage I)	4.55	3.91	5.30	–
AJCC stage IV (referent group: stage I)	1.39	0.88	2.18	–
AJCC stage not classified	1.10	0.81	1.51	–
Constant	0.40	–	–	<0.01

Goodness of fit $\chi^2 = 82.64$.

AJCC: American Joint Cancer Committee; ARIA: Accessibility Remoteness Index of Australia.

clinical trials. We found that AJCC stage of disease at initial presentation was the strongest predictor of melanoma clinical trial participation, and neither SES, remoteness nor proximity to the MIA were significant factors when adjusted for relevant covariates. Reporting of the SES of trial participants enables judgments to be made regarding the generalizability of trial findings.

Future perspective

In order to ensure the generalizability of the results from melanoma clinical trials, there will be greater recognition of the importance of recruiting a wide range of subjects with differing sociodemographic and clinical characteristics. If this is not adequately achieved, then extensive

modeling based on data from unselected cohorts will be required. More trials will be offered to older people and those with stage IV melanoma than is currently the case.

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