Melanoma Management

Original Research Article

Title: The impact of socio-economic status on melanoma clinical trial participation: an observational cohort study from Australia.

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Summary: Low socio-economic status (SES) is reported to be a barrier to participation in cancer clinical trials due to out-of-pocket costs associated with trial participation, logistical barriers to attend screening services in different diagnostic and treatment centers, and associated cultural or linguistic barriers. One study of clinical trial participation in the ocular melanoma population, reported somewhat different results, whereby people of an older age (≥60 years), lower education level, and those with non-managerial jobs were more likely to participate in a clinical trial, than their younger, more educated counterparts. The aim of the present study was to determine whether SES was associated with participation in clinical trials for people with cutaneous melanoma.

Keywords: melanoma, clinical trials, socio-economic status, equity, participation

Future perspective: To ensure 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 socio-demographic and clinical characteristics. If this is not adequately achieved then extensive modelling 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.

Executive summary:

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
- To ensure generalizability of results from clinical trials, a wide range of subjects need to be recruited
- People of low socio-economic 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 (MIA), and assessed factors affecting melanoma clinical trial participation using logistic regression

Factors predicting clinical trial participation

- Clinical trial participation occurred in 2338 of 10350 patients (23%), with surgical trials recruiting the largest number of participants (1454, 62%)
- Multivariate analyses showed a lower likelihood of trial participation with each year of increasing age (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 presenting with AJCC stage II or III disease were much more likely to participate than patients with stage I disease (OR 2.81, 95%CI2.50-3.16, and OR 4.55 95%CI 3.91-5.30)
- SES did not affect trial participation

Implications for policy and practice

- Identification of 'low participation' groups can help tailor recruitment strategies to ensure representative participation of those 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 about the generalizability of the trial findings

Abstract

Aims: To determine whether socio-economic status (SES) is associated with participation in melanoma clinical trials.

Materials & Methods: Retrospective single-center observational study conducted at Melanoma Institute Australia (MIA). Factors affecting clinical trial participation were assessed using logistic regression.

Results: Of 10350 patients, 2338 (23%) participated in a clinical trial. Multivariate analysis indicated males compared to females, OR 1.18, (95%CI 1.07-1.30), and patients with AJCC 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, (2.50-3.16) and OR 4.55, (3.91-5.30). SES did not affect trial participation.

Conclusion: Our data suggest SES was not a significant predictor of melanoma clinical trial participation when adjusted for other factors.

Introduction:

Cutaneous melanoma imposes a heavy burden of morbidity and mortality on fair-skinned populations worldwide. The use of clinical trials to evaluate the efficacy of new treatments is fundamental to guide future clinical practice and improve 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.[1-4] To ensure generalizability of results from clinical trials, a wide range of subjects need to be recruited. This includes variation in patient and disease-related characteristics including participant age, sex, socio-economic status, geographic residence, melanoma sub-type, genetic factors, comorbid conditions and sun protection behaviours.

People of low socio-economic status have been reported to miss out on the opportunity to participate in clinical trials.[5] 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 generalise the results to all sectors of the community. In the past, melanoma was considered to be a disease that affected more affluent populations, however recently there has been a rise in the incidence of melanoma in the more socially deprived areas of the UK[6] and poorer coastal towns in Australia.[7] In fact in 2011, 9 of the 10 local government areas with the highest standardised incidence ratio of melanoma in New South Wales, Australia, were in areas of relative socio-economic disadvantage.[7]

Low socio-economic status has been reported to be a barrier to participation in clinical trials of other cancers due to several factors including costs associated with trial participation, eg. additional specialist visits or out-of-pocket payments for diagnostic tests; [8,9] logistic barriers to attending multiple services in multiple centers, particularly for assessment of trial eligibility (screening);[10,11] and associated cultural or linguistic barriers.[12,13] The one study of trials 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 non-managerial jobs were more likely to participate in a clinical trial, than their younger, more educated

counterparts.[14] The aim of the present study was therefore to determine whether socio-economic status (SES) was associated with participation in clinical trials for people with cutaneous melanoma. Our hypotheses were (i) that low SES was negatively associated with trials participation; and (ii) that close proximity to the trial center was positively associated with participation. Our research report follows the format of the 'Strengthening the reporting of observational studies in epidemiology' (STROBE) statement.[15]

Patients & methods:

Study design

We conducted a retrospective, single center observational study among consecutive patients of Melanoma Institute Australia (MIA) diagnosed with cutaneous melanoma between 1st January 1995 and 31st December 2010. Based in Sydney, New South Wales, 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 behavioural 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. Information collected included demographic data, detailed clinical treatment, diagnostic investigations, clinical trial participation including trial type, follow-up consultations and relevant melanoma and general health outcomes.

Patients of any age with a biopsy proven melanoma (either *in situ* or *invasive* cutaneous melanoma) and any AJCC stage of disease 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 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 non-randomized and could involve an intervention from any discipline or combination of disciplines (for example, surgery and immunotherapy). Explanatory variables included patient characteristics such as age at melanoma diagnosis, sex, SES, country of birth, marital status, residential address, year of diagnosis; as well as tumor characteristics such as Breslow thickness, ulceration, histopathological sub-type, tumor mitotic rate, anatomical body site, AJCC stage of disease at first 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, described in detail below.[16]

Three variables for SES and access to healthcare were used. 1) The Index for Relative Socio-economic Advantage and Disadvantage which categorises census collection districts (small areas of approximately 200 similar households) across Australia into deciles of increasing SES, known as SEIFA scores. 2) The Accessibility Remoteness Index of Australia (ARIA), which allocates a remoteness index between 1 (metropolitan cities) to 5 (very remote area), on the basis of access to essential services. 3) 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 (http://www.gpsvisualizer.com/geocode). Second, a specialised mapping software program (ArcGIS, http://www.esri.com/software/arcgis) 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 which was then attributed to each patient. Finally, the Euclidean or straight line distance between the patients' residence and MIA was calculated using the ArcGIS software's spatial analyst function, and reported in kilometers.

Statistical methods

Our analyses were designed to examine the relevance of socio-economic status 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 kilometres were treated as continuous variables. AJCC stage of disease was treated as a categorical variable with the stage 0, or stage I as referent groups. Following univariate analyses and consideration of confounding factors, a backward stepwise method was used to construct logistic regression models, where variables that had a p-value greater than 0.25 were excluded. The first binary logistic regression model contained all patients meeting our inclusion criteria. The second model excluded patients with *in situ* melanoma (AJCC Stage 0). 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 for the likelihood of participating in a melanoma clinical trial. Ratios with a p value of <0.05 were considered statistically significant.

Results: Between 1995 and 2010, 10350 patients including 9074 with invasive melanoma were identified, mean age 57 years, 55% males. The majority of patients (77%) were AJCC stage I or II at presentation, and the median Breslow tumour thickness was 0.98mm. (Table 1) The median distance between the patient's home and MIA was 26 kilometres (interquartile range 12-82), over three quarters of the patients lived in metropolitan cities, with the majority (83%) from areas of medium to high SES. Patients resided in all states in Australia, but most were from New South Wales. The median follow-up for the whole group was 34 months (IQR 12-72) with 1241 of 10350 patients (12%) lost to follow-up at final recording of melanoma status.

Clinical trial participation occurred in 2338 of 10350 patients (23%), with surgical trials recruiting the largest number of participants (1454, 62%). (Table 2) Over 1000 AJCC stage I patients and 794 stage II patients were enrolled in trials over the 15 year study period.

Univariate logisitic regression analyses for the whole group showed that patient age, sex, SES, remoteness index and AJCC stage of disease were significant predictors of clinical trial participation. Of note, people from areas of higher

SES were slightly *less* likely to participate than people from areas of low SES. Multivariate analyses for the whole group showed increasing age was associated with a lower likelihood of trials participation (OR 0.99, 95%CI 0.98-0.99), males were more likely to participate than females (OR 1.18, 95%CI 1.07-1.31), and patients presenting with invasive melanomas (AJCC stage I-IV) were much more likely to participate than patients with in situ melanomas (ORs 8-37, 95%CIs 5.73-53.20).(Table 3) While there was a trend for patients from more remote areas compared to less remote areas of Australia to participate in trials this was not statistically significant (p=0.05). SES status was no longer a significant predictor of participation (p=0.78).

For patients with primary invasive melanomas only (n=9074) similar results to the whole group were seen in univariate analyses (data not shown). Multivariate analyses showed a lower likelihood of trial participation with each year of increasing age (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 presenting with AJCC stage II or III disease were much more likely to participate than patients with stage I disease (OR 2.81, 95%CI2.50-3.16, and OR 4.55 95%CI 3.91-5.30) respectively.(Table 4) 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). Neither SES, geographical remoteness nor distance from the MIA significantly predicted clinical trial participation for patients with invasive melanoma.

Discussion:

This is the largest study about melanoma clinical trial participation reported to date, as far as we are aware. Our data suggest almost one quarter of all patients attending MIA participate in clinical trials. We found that AJCC stage of disease was the strongest predictor of melanoma clinical trial participation and neither SES, remoteness nor proximity to 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 to findings from other cancer centers in the United States, where typically one in 20 patients are enrolled in trials.[17] In the United Kingdom, the National Cancer Research Institute has reported that over the last decade participation in clinical studies has increased from one in 26 to one in 6 diagnosed patients.[17] In Australia the national cancer agency (Cancer Australia) has provided substantial funding to increase cancer trial participation rates, with a specific focus on culturally and linguistically diverse groups and those from rural or remote areas.[18] The high rate of recruitment at 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 Institute, along with the necessary personnel and expertise to accommodate clinical research. Overall, our findings were similar to those reported in the COMS ocular melanoma study[14] in that low SES was not a barrier to clinical trials participation.

Limitations

Our dataset 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 socio-economic indicators such as number of bedrooms, equivalized household income, proportion of people in professional or managerial occupations, proportion of adults who have attended university, car ownership, and broadband internet access. One potential issue with the use of this variable is misclassification of individuals. For example, people of relative social advantage who choose to reside in an area of disadvantage may be classified as low SES. Our strategy to minimise 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 4,000 households. As an aside, the census collection district boundaries in Australia changed between 2001 and 2006,[16] resulting in a few residential addresses that changed 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, MIA, which has a substantial clinical trials infrastructure and acts as a tertiary referral center. 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.

Interpretation

Our findings contain important messages for melanoma clinicians and research staff. Firstly, when screening potential clinical trial candidates and discussing trial eligibility, it is important to consider people of all socio-economic 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. Secondly, consider that upper age limits may exclude older people who may have otherwise adequate performance status, and are willing to be involved.[19] 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. Thirdly, ensure that clinical trials for all stages of melanoma including stage IV disease are open and available for patients. This may require 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 (http://www.australiancancertrials.gov.au/) and the Cancer Council NSW provide a useful list of trials by center, including those open to recruitment, that 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.[20] For cancer patients the evidence is less clear,[21]

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 treatment for future patients. Identification of 'low participation' groups can help tailor recruitment strategies to ensure representative participation of those affected by melanoma. We encourage the reporting of the SES of trial participants to enable judgments to be made about the generalizability of the trial findings.

Further research is needed 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.

Conclusions:

Our data show that a very large proportion of patients attending MIA participate in clinical trials. We found that AJCC stage of disease was the strongest predictor of melanoma clinical trial participation and neither SES, remoteness nor proximity to MIA were significant factors when adjusted for relevant covariates. Reporting of the SES of trial participants enables judgments to be made about the generalizability of trial findings.

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Table 1. Socio-demographic and tumor characteristics of study sample (n=10,350)

	Factor	n	%
Age at diagnosis of primary melanoma	Median (IQR)	57 (44 - 69)	
	<=30 years	803	7.8
	31 – 50 years	2970	28.7
	51 – 70 years	4342	42.0
	>70 years	2235	21.6
Sex	Males	5697	55.0
	Females	4653	45.0
Birth country	Australia/NZ	1516	14.6
	Outside Australia	4533	43.8
	Not documented	4301	41.6
Marital status	Single	326	3.1
	Married/ de facto	1358	13.1
	Divorced/ Widowed/ Separated	93	0.9
	Not documented	8573	82.8
Socio-Economic Status	Low (SEIFA Deciles 1-3)	1761	17.0
	Medium to High (SEIFA Deciles 4-10)	8589	83.0
ARIA (Remoteness Index)	1 (Metropolitan cities)	8000	77.3
	2 (Inner regional)	1748	16.9
	3 (Outer regional)	564	5.4
	4 and 5 (Remote and very remote)	38	0.4
Distance between home and melanoma clinic (km)	Median (IQR)	25.8 (11.6 - 82.0)	
	<=10	2228	21.5
	10.1 – 30	3311	32.0
	30.1 – 100	2541	24.6
	100.1 – 400	1793	17.3
	>400	477	4.6
Melanoma Subtype	Acral lentiginous	84	0.8
	Desmoplastic melanoma *	565	5.5
	Melanoma in situ **	1276	12.3
	Lentigo maligna melanoma	399	3.9
	Superficial Spreading Melanoma ***	4220	40.8
	Nodular Melanoma	1613	15.6
	Mixed ****	2193	21.2
AJCC Stage	Stage 0 (in situ)	1276	12.3
	Stage I	5543	53.6
	Stage II	2268	21.9
	Stage III	876	8.5
	Stage IV	115	1.1
	Unclassified	272	2.6
Breslow Thickness (mm)	Median (IQR)	0.98 (0.44 - 2.00)	
	0.0 (in situ)	1276	12.3
	0.01 – 1.0	4028	38.9
	1.01 – 4.0	3748	36.2
	>4.0	900	8.7
	Not documented	398	3.8
Last Follow-up Status	Alive, no sign of recurrence	7381	71.3
	Alive, status unknown	144	1.4
	Alive, with melanoma	316	3.1
	Dead, cause unknown	235	2.3
	Dead, melanoma	904	8.7
	Dead, not melanoma	129	1.2
	Lost to follow-up	1241	12.0

* Desmoplastic melanoma (pure+with neurotropia) | ** Melanoma in situ (pure+with dysplastic naevi) |

*** Superficial Spreading Melanoma (pure+with HMF+with NM) | **** Mixed+Occult+Malignant blue naevus+ Unknown

SEIFA – Socio-Economic Index For Areas | AJCC – American Joint Cancer Committee

Table 2. Clinical trial type by AJCC stage of disease

	AJCC Stage of disease													
	Stage 0		Stage I		Stage II		Stage III		Stage IV		Stage Unknown		Total	
Clinical Trial type	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Chemotherapy	--	--	7	11%	22	34%	25	38%	3	5%	8	12%	65	3%
Follow-up of melanoma	2	3%	66	85%	8	10%	2	3%	--	--	--	--	78	3%
Immunotherapy	1	1%	26	27%	24	25%	41	42%	2	2%	3	3%	97	4%
Pathology / Tumour bank	29	6%	216	42%	147	28%	90	17%	11	2%	26	5%	519	22%
Psychosocial outcomes	1	2%	38	60%	14	22%	9	14%	--	--	1	2%	63	3%
Radiotherapy	--	--	12	23%	16	30%	20	38%	4	8%	1	2%	53	2%
Surgery	1	0%	638	44%	561	39%	238	16%	3	0%	13	1%	1454	62%
Surgery / Chemotherapy	--	--	--	--	1	25%	2	50%	1	25%	--	--	4	0%
Unknown	--	--	--	--	1	20%	3	60%	1	20%	--	--	5	0%
Total	34	1%	1003	43%	794	34%	430	18%	25	1%	52	2%	2338	100%

Table 3. Multivariate logistic regression for factors predicting clinical trial participation in patients with insitu or invasive melanoma (n=10,350)

Factor	Odds Ratio	95% CI		P value
		Lower	Upper	
Age at primary diagnosis (years)	.99	.98	.99	<.01
Sex (males vs females)	1.18	1.07	1.31	<.01
Socio-Economic Status (deciles 1-10)	1.00	.98	1.02	.70
ARIA Remoteness Index (quintiles 1-5)	1.11	1.00	1.23	.05
Distance from home to MIA (km)	1.00	.99	1.00	.05
AJCC Stage (Referent: Stage 0)				<.01
Stage I	8.12	5.73	11.50	
Stage II	22.60	15.86	32.22	
Stage III	36.84	25.51	53.20	
Stage IV	11.20	6.38	19.67	
Stage Not Classified	8.94	5.66	14.13	
Constant	.05			<.01

χ^2 103.83

Table 4. Multivariate logistic regression for factors predicting clinical trial participation in patients with invasive melanoma only (n=9,074)

Factor	Odds Ratio	95% CI		P value
		Lower	Upper	
Age at primary diagnosis (years)	.99	.98	.99	<.01
Sex (males vs females)	1.18	1.07	1.30	<.01
Socio-Economic Status (deciles 1-10)	1.00	.98	1.02	.78
ARIA Remoteness Index (quintiles 1-5)	1.10	.99	1.22	.07
Distance (km)	1.00	1.00	1.00	.06
AJCC Stage (Referent group: Stage I)				<.01
Stage II	2.81	2.50	3.16	
Stage III	4.55	3.91	5.30	
Stage IV	1.39	.88	2.18	
Stage Not Classified	1.10	.81	1.51	
Constant	.40			<.01

χ^2 82.64