MINIREVIEW

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The impact of socioeconomic status on access to cancer clinical trials

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Cancer clinical trials enable the development of novel agents for the potential benefit of cancer patients. Enrolment in a trial offers patients the chance of superior efficacy coupled to the risk of unanticipated toxicity. For trial results to be generalisable, the data need to be collected in patients' representative of the general cancer population. Socioeconomic deprivation is associated with poor cancer outcomes. In the developed world, the gap between the most and least deprived is widening. This mini-review explores the evidence regarding socioeconomics and access to cancer trials, highlighting the underrepresentation of deprived patients, and exploring reasons for this disparity.

Although worldwide life expectancy is improving, the gap in life expectancy between the most and least affluent is widening in the developed world (Thomas *et al*, 2010; Krieger *et al*, 2012). This separation may largely be driven by the health impact of high-risk lifestyle activities such as smoking, poor diet and inactivity, which vary in prevalence by socioeconomic status (SES). However, differential access to care, especially in countries where universal health care is not the norm, may also be a dominant factor in SES-related life expectancy disparities (Disparities in cancer care, 2006). Cancer care is similarly subject to the same SES-related health disparity factors (2006). The burden of cancer care on lower SES populations is increased, they are less likely to attend cancer screening programmes, and suffer from poorer outcomes (2006; Renshaw *et al*, 2010; Herndon *et al*, 2013). As interventional clinical research is integral to much of modern cancer care, in this review we explore ways in which access to cancer clinical trials (CCTs) may be influenced by common health and sociodemographic inequalities.

While the exposure of patients to effective novel treatments is a benefit of clinical trials, this must be balanced against the fact that in randomised studies patients may experience greater inconveniences (trips, tests, etc.) simply to acquire the standard of care and many studies of agents show either no benefit or worsened outcomes compared with standard of care therapies. Of note, the level of negative clinical research outcomes may be underestimated in practice due to publication bias in favour of CCTs reporting positive outcomes (Tam *et al*, 2011). However, evidence supports RCTs offering at least equivalence to standard treatment (Gross *et al*, 2006), and enrolment of patients in CCTs is considered by physicians to be of value and importance (Somkin *et al*, 2005). If we accept the premise that CCTs are overall of benefit to patients and the advancement of cancer care, then they should, in theory, be offered to all eligible patients for reasons of equity. In addition, for CCTs to deliver conclusions that are applicable in practice they should be drawn from populations for whom the treatment is intended. In an ideal world the mix of patients in clinical trials should reflect the mix of patients receiving treatment for cancer in general.

EVIDENCE OF UNEQUAL ACCESS TO CLINICAL TRIALS IN RELATION TO SES

In the United States recognition of disparities in clinical trial access has lead to national policy strategies. In 1993, the National Institutes of Health (NIH) passed the 'Revitalization Act' stating that women and minorities must be better represented in clinical research. In keeping with this, the Federal Drug Administration (FDA) began mandating gender analysis in clinical trial data and reversed its requirement that women of childbearing age be excluded from early phase trials. Between 1993 and 2002, the budget of the National Cancer Institute (NCI) doubled, with an associated significant rise in NCI CCT accrual to 2.5% (Shavers and Brown, 2002). In the United Kingdom, the creation of the National Cancer Research Network (NCRN) has seen recruitment to cancer research studies rise from 3.7% to 17% of newly

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diagnosed cancer patients between 2001 and 2011. Despite this progress, minorities, the elderly, adolescents, patients from rural communities, and (in regions without universal health care) the uninsured remain underrepresented (Kwiatkowski *et al*, 2013).

With regard to SES, Sateren *et al* (2002) examined the accrual of patients to NCI-sponsored clinical trials over a 1-year period. They found that higher socioeconomic levels were associated with an increased accrual to clinical trials. Associated factors included: income (increase of 0.7 patients per $1000 increase in mean income); poverty (decrease of 0.32 patients per 1% increase in population in poverty); education level (increase of 1.51 patients per 1% increase in population with a college degree); and employment (decrease of 0.7 patients per 1% increase in unemployment). They also noted that patients enrolled onto clinical trials were less likely to be uninsured, and more likely to have Medicare (in 2000 Medicare policy was changed to cover the routine costs of trial participation). Data from Maryland between 1999 and 2002 revealed lower accrual to trials with increasing deprivation scores. Those enrolled were less likely to be uninsured, or covered by Medicaid or private insurance, compared with the general population. Recruitment was found to be associated with social class (Baquet *et al*, 2008).

Income was also notably associated with trial participation in an internet-based survey of 5499 patients asked about their cancer treatment decisions (Unger *et al*, 2013). Among the survey respondents, both discussion of a trial and subsequent participation were associated with being younger, wealthier, and more highly educated.

Both education attainment and wealth estimates are most commonly used in models of SES. Education alone is also considered as a valid surrogate of SES (Herndon *et al*, 2013). In a survival analysis of 6166 breast cancer patients enrolled in clinical trials conducted between 1987 and 2003 by the Cancer and Leukemia Group B collaborative research group, only 12% of those enrolled onto trials did not have a high school diploma, in comparison with 31% nationally (Alliance for Excellent Education, 2009) suggesting significant underrepresentation of patients with lower educational levels in these trials. In addition, even among those enrolled on trials lower educational attainment was associated with poorer outcomes (Herndon *et al*, 2013).

In the setting of early phase cancer trials there is evidence that referral is biased significantly in favour of the more affluent population, with enrolment on a trial after contact with the trials clinic not affected by SES (Mohd Noor *et al*, 2013). In another US-based study, patients of moderate-to-high SES were over-represented. Only 5% had not graduated from high school (cf 31% nationally), and 24% had postgraduate degrees. In all, 11% had a household income of less than $25 000 in comparison with a figure of 25% nationally in 2011 (US Department of Commerce, 2011).

SOCIOECONOMIC REASONS FOR LOW RECRUITMENT

Patient factors. Lack of education about cancer and CCTs is a frequently reported barrier to trials access (Mills *et al*, 2006; Ford *et al*, 2008). Less readily defined are aspects of culture and belief that influence patient decision-making. When considering under-representation of African Americans (AAs) in CCTs the impact of the Tuskegee syphilis study on trust in medical research is often cited (Corbie-Smith, 1999). It is notable that this may lead to assumptions about willingness to participate, exacerbating recruitment bias. Therefore, it is important to note that surveys of cancer patients in regions of the United States do report equal willingness to participate in CCTs among AAs, Hispanics, and whites, despite a greater reported fear of participation in randomised trials (Byrne *et al*, 2013). A synthesis of the available literature on AA patients' participation in cancer prevention, screening, and intervention trials found five elements key to CCT participation: negative beliefs about trials, lack of knowledge, influence of faith, health-care provider influence, and friends' or relatives' participation in CCTs, or recommendations (Rivers *et al*, 2013). Addressing these complex social barriers likely requires tailored community engagement. The use of ethnicity as a variable to examine underrepresentation of other groups of patients in CCTs is emerging as an oversimplification. There is growing evidence that outcome differences attributed to race may in fact be more dependent on SES (Du *et al*, 2008), with SES a key barrier to enrolment (Sateren *et al*, 2002). Consideration of both race and SES when addressing inequality enables clearer delineation of true barriers within communities.

Many CCTs mandate a certain level of global fitness, as well as standard measures for organ function. Multiple co-morbidities associated with poor pre-cancer health may negatively impact on a patient's ability to meet these protocol mandated criteria. Education level, as a surrogate of SES, has been shown to inversely correlate with leading causes of death, and as noted in the CALGB trial with worsened outcomes within clinical trials (Jemal *et al*, 2008). These eligibility criteria barriers are a frequently cited cause of non-participation for underrepresented populations in CTCs (Mills *et al*, 2006; Ford *et al*, 2008). It has been reported that people from lower socioeconomic groups are less likely to attend for cancer screening programmes, and present at later stages of disease (Ionescu *et al*, 1998; Renshaw *et al*, 2010). Certainly, late presentation, and late initial therapy, could increase the risk of co-morbidity hindering recruitment to trials.

The information offered about clinical trials may be in an inappropriate form for many except those patients with high educational attainment. The language used in patient information and consent forms has long been a concern: a study in 2003 found that consent forms consistently failed readability guidelines, with language complexity hindering understanding for people with low reading levels (Paasche-Orlow *et al*, 2003). This inevitably affects those with lower educational attainment disproportionately, and may result in refusal to participate in trials. In areas or groups in which minority languages are commonly spoken, with the assumption that these may be more associated with lower SES, ease and speed of access to translators and to either long or short form translated consent forms may be an additional factor influencing relevant communication about clinical trials.

Financial concerns are of relevance even in areas with universal health care such as the United Kingdom. Hidden costs, such as travel to and from clinics, the need for extra childcare, and the loss of income due to missed work will be more significant for those of lower SES. These costs are compounded in areas with no universal health-care provision by concerns about insurance coverage of participation in clinical trials, or indeed about whether any care is available where the patient is uninsured. In the United States, indigent insurance programmes may restrict care to specific hospitals in the region, which may not be the same hospitals with thriving clinical research programmes. Indeed, in the United States and many countries, clinical trials are not universally distributed across geographic areas. For example, US national level for lung cancer patient enrolment in clinical trials is $\sim$3%, but in some NCI-designated cancer centres accrual rates, which are highly clustered in key urban populations, may reach ten times this value. More affluent populations may be more likely to seek out physicians at centres with clinical trial portfolios. While patients with good insurance may choose to travel they still need accurate information on where specific novel therapies may be available (West and Camidge, 2012). National trials registry sites such as www.clinicaltrials.gov do exist, but their ease of use is questionable for those with lower educational levels. Financial coercion via compensation for trial participation may disproportionately affect

poorer patients—if you are wealthy being paid to participate is not an incentive—for this reason inclusion of financial incentives in CTCs is rarely considered as ethical.

Health-care professional factors. To be initially referred for consideration of a trial, the referring clinician must consider the patient a candidate. There are several reasons why they may not do so. First, as mentioned above, the patient may suffer from multiple comorbidities, which the clinician seen as incompatible with clinical trial involvement. Second, the clinician may be unaware of a trial that is applicable for the patient, so that trial access becomes dependent upon the patient's motivation and access to information. Third, the clinician may make decisions, either consciously or sub-consciously, about the appropriateness of referral for a trial based on assumptions about their socioeconomic characteristics. Physicians in specialist centres are more orientated towards research than those based in community general hospitals (Ford *et al*, 2011). Physicians are more likely to refer patients for CCTs than surgeons (Klabunde *et al*, 2011). In early phase CCTs, SES has been shown to be a clear barrier to referral (Mohd Noor *et al*, 2013). In addition, it is of concern that clinicians' preconceptions about patients' willingness or ability to participate may be a contributing factor. A cancer patient's initial treating specialist, surgeon or physician, therefore, has a very important and influential role in their care. A lack of understanding of CCTs, or a wariness about trials on the clinician's part has the potential to impact significantly on referral, but also on patient attitudes to trial enrolment (Mills *et al*, 2006). Education about trials in general and available CCTs in particular is key to overcoming referrer bias, as is a focus on communication skills for front-line clinicians. (Ford *et al*, 2011). More directed strategies to overcome referrer barriers to CCT access are complex, and in practice prove difficult to deliver (Michaels *et al*, 2012). A final clinician-driven obstacle to enrolment is the complex nature of CCTs. A clinician may not have time to provide adequate explanation and counseling about the trial, particularly in for-profit private practice models in some countries. Given these time constraints, often it may simply be 'easier' for the clinician to only counsel more educated patients about trials.

SOLUTIONS TO THE PROBLEM

Improving the access of patients from lower socioeconomic groups to cancer screening, diagnosis and therapy will increase their representation on clinical trials. General health-care policy such as national smoking cessation programmes and alcohol awareness campaigns will go some way to decrease the levels of comorbidities disproportionally affecting lower socioeconomic groups. These are, however, long-term national strategies not influenced by clinical trial stakeholders. Improving the recruitment from the current pool may be affected through improved communication, both between health-care professional and patient, and from clinical trial investigators to referring physicians.

Social and cultural barriers can and have been addressed by innovative approaches; prostate cancer screening information in AA barber shops, flexible timing of screening interventions for busy working mothers and educating clergy to address barriers to cancer care to name but a few (Sadler *et al*, 2001; Hart *et al*, 2008; Germino *et al*, 2011). These approaches are labour intensive, potentially costly and may only access small populations, however, multiple small solutions to this large problem could be the way change is affected.

It is important that all patients are considered for clinical trial enrolment, and that any exclusion from recruitment is based upon trial entry criteria. To that end referring clinicians should be made aware of all potential trials available. Proactive strategies to encourage referral of patients from lower SES groups may be of benefit, but are challenging to implement (Michaels *et al*, 2012). For patients with low reading levels, a video presentation rather than written material may be useful (Unger *et al*, 2013). Improved readability of leaflets with simple language may help in conveying complex concepts to all patients regardless of education level. From 2014, all insurance providers in United States will be obliged to cover standard costs of clinical trials. This step will hopefully make CCTs more desirable to US cancer patients. Where the cost of travel is a limitation, satellite clinics closer to patients' homes, as well as expanding portfolios of trials in rural practice settings away from large cancer centres, may improve access for more deprived populations.

Finding methods to engage minority groups with cultural sensitivity is key to helping reduce the impact of pre-conceptions among underprivileged groups regarding safety and applicability of CCTs (Germino *et al*, 2011). The use of patient navigators with training in cultural barriers prevalent in the communities they serve may help overcome some of the patient-derived obstacles to CCT enrolment.

Finally, health-care professionals must address their own communication abilities. Full and clear communication is better for patients. Infrastructure needs to be in place to ensure discussion of CCTs is possible within the clinical framework, to better improve communication between patients and staff. Trust is a key in care delivery, all the more so when considering enrolment in a trial.

CONCLUSIONS

Under representation of lower SES groups in cancer trials is a pressing issue for cancer researchers. Improving CCT access for these groups has been a key policy issue internationally for some time. There is a large literature on barriers to CCTs, and on strategies to improve accrual. Organisational approaches to improve CCT access have begun to produce results, but largely just in total numbers recruited to trials, with little impact seen on inequalities. There is still some way to go before the benefits and burdens of CCTs are born by truly representative patient populations.

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