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Response to comment on 'Existing prognostic models, but not neutrophil-to-lymphocyte ratio, are prognostic in malignant mesothelioma'

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Sir,

Our goal when this study was designed was to understand whether the findings of the initial study (Kao *et al*, 2010) could also be useful at other clinical time points, and whether neutrophil-to-lymphocyte ratio (NLR) retained independent significance when established clinical prognostic factors were incorporated. The data did not support our initial hypothesis, and the correspondents take issue with this (Kao *et al*, 2014). The validation of prognostic markers in retrospective series frequently generates conflicting findings, and we all await a robustly designed prospective study to resolve this controversy.

The correspondents suggest that our study was flawed due to the inclusion criteria that they considered were arbitrarily defined and that led to selection bias. We acknowledge that this is an inherent limitation of all retrospective studies, including previous studies of the NLR. In the initial study (Kao *et al*, 2010), only patients receiving systemic therapy were selected, and 61% were selected due to their participation in clinical trials. Subsequent studies selected only patients undergoing extrapleural pneumonectomy (EPP) (Kao *et al*, 2011) or only patients with occupational dust exposure seeking compensation from the Dust Disease Board (Kao *et al*, 2013). In a fourth study, patients were excluded if they had a history of inflammatory disease, a second primary, active infection or insufficient follow-up data (Pinato *et al*, 2012). These were therefore also studies with heterogeneous patient populations receiving different treatment approaches.

We set out to validate NLR at diagnosis and at the time of starting treatment, using pre-specified selection criteria and therefore screened all consecutive patients where: (a) the disease under study was confirmed, (b) the variable under study was available and (c) there were no co-existing confounders that may influence the disease or variable under study. It would not be possible to validate the prognostic significance of NLR in patients where the target biomarker was unknown, and we therefore maintain the appropriateness of our selection criteria, and have transparently reported the study denominator. Moreover, all other missing data were described in our report, and the resulting multivariate model was the first published NLR study to include previously established clinical and laboratory prognostic variables. Our data were analysed using rigorous statistical methodology, including the consideration of missing data by multiple imputation.

Kao *et al* maintain that our data showed 'unusually good overall survival', and this can be adequately refuted by referring to our paper, where we defined overall survival (OS) as being calculated from the time of diagnosis, but also provided OS from the time of commencement of systemic therapy. This was 12.3 months for all patients receiving chemotherapy and 11.7 months for those treated with chemotherapy only (that is, non-surgically). This OS does not differ materially from an OS of 12.1 months for the intervention arm of the landmark cisplatin/pemetrexed study (Vogelzang *et al*, 2003) and an OS of 11.7 months for the chemotherapy-naive group of the initial study of NLR in MPM (Kao *et al*, 2010).

The results were indeed not what we had originally anticipated; nevertheless, we have pursued the scientifically and ethically appropriate course of reporting 'negative' results, which are contradictory to others' findings. Failure to publish negative findings can lead to substantial publication bias in retrospective analyses of data. Our data were subjected to rigorous statistical methodology and we have reported what we found. Furthermore, the NLR cut-off was not data driven but selected *a priori* on the basis of the correspondents' own published literature. In our discussion, we cautioned against data-driven cut-offs and note that the NLR literature is not consistent in choice of cut-point, which may also have resulted in contradictory findings across studies. Kao *et al* refer to other manuscripts confirming the prognostic value of NLR that were published during the period in which our manuscript was in submission and in press and that continue to inform scientific debate. At the time of submission we were not privy to these data, which may reflect either an increasing literature on the importance of NLR or alternatively a positive publication bias in retrospective series.

We acknowledge Kao *et al* as the initiators of this field in mesothelioma and, as previously stated, had anticipated confirming their initial study (Kao *et al*, 2010) in an additional cohort. That we were not able to do this is not a repudiation of the potential value of NLR, but an invitation for additional rigorous prospective research in the field to fully define the place of this potential prognostic marker.

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Comment on 'Interventions to improve exercise behaviour in sedentary people living with and beyond cancer: a systematic review'

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Sir,

We read with great interest the review by Bourke *et al* (2014). We agree there is a dearth of evidence that any specific intervention results in improved adherence to physical activity guidelines in cancer patients and survivors but would like, respectfully, to offer some further observations.

The authors, in our view, could distinguish more clearly between 'Physical Activity' and 'Exercise' and acknowledge that 'sedentary behaviour' can be independent of physical activity levels. The terms 'exercise behaviour' and 'physical activity' are not interchangeable. 'Physical Activity' refers to body movement produced by the contraction of skeletal muscles and that increases

energy expenditure. 'Exercise' refers to planned, structured and repetitive movement to improve or maintain one or more components of physical fitness (Chodzko-Zajko *et al*, 2009). So a person may take little exercise but be physically active with low levels of sedentary behaviour, whereas another might do structured exercises but be habitually inactive and spend long periods sedentary. Thus, the end points of some of the reviewed trials and the methods used to measure those end points require more critical discussion. For example, the authors acknowledge that aerobic exercise tolerance may not reflect aerobic fitness – but neither of those necessarily translates into improved habitual physical activity. The authors acknowledge the challenge of achieving current physical activity guidelines, but do not mention potential end points at the lower end of the physical activity continuum – for example, breaking up sedentary behaviour with light activity – which may be critical in cancer survivors, given recent recognition of the adverse health consequences of high levels of sedentary behaviour in cancer populations (Lynch *et al*, 2013).

We would also like to draw particular attention to differences between the reviewed studies in the methods used to measure physical activity end points, such as self-report measures, heart rate monitors and accelerometers. Two studies (Pinto *et al*, 2005, 2013) included in the analysis showed that self-report measures did not correspond with objectively measured physical activity, which we also found in both an observational (Broderick *et al*, 2013b) and an intervention study (Broderick *et al*, 2013a). Unless sedentary behaviour and all physical activity, including exercise, are accurately, consistently and objectively measured across studies, using, for example, accelerometers, we think it will be impossible to answer the 'million dollar' question of how best to improve habitual physical activity and adherence to guidelines for health benefits in cancer patients and survivors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Response to comment on 'Interventions to improve exercise behaviour in sedentary people living with and beyond cancer: a systematic review'

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Sir,

We thank Broderick *et al* (2014) for their interest in our manuscript. We agree there seems to be uncertainty in the terminology around exercise interventions, which has not been helped by the implication of a distinction between the terms 'physical activity' and 'exercise' in some publications (Chodzko-Zajko *et al*, 2009). A more constructive approach would appear to be that taken by Winter and Fowler, (2009) in defining and quantifying exercise according to the Systeme International d'Unites. As stated in the review, this is the approach we chose to follow, for several reasons:

1. An important aspect of a systematic review is to summarise the current evidence base with a view to identifying prospective research priorities or furthering practice. In this context, making a distinction between physical activity and exercise is unhelpful, particularly in evaluating clinical effectiveness. As in other clinical trials, most notably drug studies, objective documentation of the amount of the intervention that is delivered is imperative to identify dose–response curves and adverse effects. The review criteria were set to include only studies reporting such objective metrics (i.e., frequency, intensity and duration) so as to facilitate reproducibility of the intervention. Any systematic review of cancer therapies will clearly identify the target population and objectively define the intervention; exercise is no different, if we are to take its use as a therapeutic intervention seriously.
2. The term 'sedentary behaviour' is open to uncertainty, as considerable exercise may be taking place in a sedentary (i.e., seated) position—for example, rowing or cycling. We agree this needs defining, but to do so by subdividing exercise into different terms, seems counterproductive. Sedentary behaviour could be defined as anyone not achieving the recommendation to take 150 min per week of moderate-intensity aerobic exercise (Rock *et al*, 2012). However, in clinical trials involving cancer cohorts, this has frequently been defined as <90, or even <60 min per week (Pinto *et al*, 2005; Daley *et al* 2007; Cadmus *et al*, 2009; Bourke *et al*, 2014). The rationale being that there should be some scope to induce a clinically meaningful benefit from participation in the intervention. If there is not, why do we need to intervene? Nevertheless, as we concluded in the review, most individuals living with or beyond cancer would currently find current guideline targets unachievable, certainly with current published interventions. More research or a revision of the one size fits all approach is warranted. We conclude in the review that a 'dose response' might be more appropriate. This would include the suggested 'potential end-points at the lower end of the physical activity continuum.' Such recommendations might require elucidation by further data collection or an individual patient data meta-analysis for any given health outcome.
3. The tendency of epidemiological studies to imply a distinction between exercise and physical activity reflects imprecision of measurement rather than any fundamental difference. Subjective metrics of exercise behaviour, for example, metabolic equivalents derived from questionnaires (Ainsworth *et al*, 2011), are often used in these reports and we agree that objective measurement of exercise behaviour are preferable in clinical trials. Dedicated accelerometers seem an overly expensive option. Less expensive alternatives such as smartphone applications or simple heart rate monitors would be welcome where the technology is available, affordable and contextually appropriate. For individuals on prescribed medication (e.g., β-blockers) that impact the cardiovascular response to physical exertion, reliable measurement of dose–response remains a challenge.

Finally, as Jan Swammerdam's 17th century experiments demonstrated rather elegantly (Needham, 1971; Winter and Fowler, 2009), skeletal muscles neither 'contract' (i.e., reduce in volume) nor expand significantly during exercise. Furthermore, movement is neither essential nor necessary (as in isometric activity) for exercise to be taking place. What is fundamental to exercise, in the context being discussed, is skeletal muscular activity exerting force and generating a metabolic response i.e. physical activity by a different name.

We look forward to reaching consensus on the role of defined exercise interventions in the treatment of a number of cancers and agree with Broderick *et al* that consensus on terminology is an essential first step. We would encourage all practitioners in this area to follow the excellent recommendations of Winter and Fowler, which perpetuate reproducibility rather than confusion.

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