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

L Bourke1,2, D J Rosario2, L Steed1 and S J C Taylor1

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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 its 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. The term ‘sedentary behaviour’ is open to uncertainty, as considerable confusion has been generated by the use of different terms (Pinto BM, Papadonatos GD, Goldstein MG, Marcus BH, Farrell N 2013 Home-based physical activity intervention for colorectal cancer survivors. Psychooncology 22(1): 54–64.).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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**Comment on ‘KRAS-mutated plasma DNA as predictor of outcome from irinotecan monotherapy in metastatic colorectal cancer’**

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Sir,

We read with great interest the article ‘KRAS-mutated plasma DNA as predictor of outcome from irinotecan monotherapy in metastatic colorectal cancer’ published by (Spindler et al, 2013) in the December 2013 issue of the British Journal of Cancer. It is now well established that only patients with wild-type KRAS metastatic colorectal cancer benefit from treatment with an anti-epidermal growth factor receptor (EGFR) monoclonal antibody and that patients with KRAS mutant metastatic colorectal cancer do not (Karapetis et al, 2008; Douillard et al, 2010). Up until now, DNA from archival tumour tissue is used to determine KRAS mutations in clinical practice. Increased recent data indicate that circulating tumour DNA in plasma, could be a new way to analyse the somatic mutation in tumours and could be a potential biomarker to ensure optimal treatment (Murtaza et al, 2013). Spindler et al (2013) aimed to investigate the clinical implication of KRAS and BRAF mutations in both archival tumour tissue and plasma cell-free DNA in 211 metastatic colorectal cancer patients treated with second-line irinotecan monotherapy. Authors observed that plasma KRAS mutations, but not tumour KRAS mutations, were associated with worse disease control rate, progression-free survival and overall survival. However, contrary to what is mentioned in the title, the predictive impact of the plasma KRAS and BRAF mutations for the irinotecan response treatment cannot be evaluated in this study because there is no control arm (patients receiving other therapies or no therapy).

In this study, KRAS mutations have been detected less frequently in plasma (31%) as compared in tumour (45%) (16 patients with a wild-type KRAS plasma had a mutation in the tumour). Tumour KRAS mutations were analysed in formalin-fixed paraffin-embedded tissue obtained at diagnosis, whereas plasma KRAS mutations were analysed in pretreatment blood samples before the beginning of second-line irinotecan monotherapy. The description of patients receiving an anti-EGFR in first-line therapy would be an interesting information, as acquired KRAS mutations can be induced by these therapies (Misale et al, 2012). The presence of a minority subclone harbouring KRAS mutations within tumours might explain the secondary resistance to anti-EGFR therapy (Tougeron et al, 2013) and the emergence of plasma KRAS mutations (Diaz et al, 2012).

Furthermore, the discordance for the KRAS mutation detection rate between tumour and plasma could be explained by a lack of sensitivity for the plasma KRAS mutations detection or by the absence of circulating tumour DNA for some patients. The amplification refractory mutation system-quantitative PCR (ARMS-qPCR) methodology, used in this study, has a sensitivity around 0.1% (Fox et al, 1998; Nordgård et al, 2012). Some studies have suggested that ARMS has an insufficient sensitivity to detect low levels of KRAS mutation (Nordgård et al, 2012). Indeed, the level of circulating tumour DNA in plasma can be very low and may represent only a small fraction of the total circulating DNA (<0.01%) (Diehl et al, 2008; Taly et al, 2013). Techniques with very high sensitivity for circulating tumour DNA detection have been recently developed (Taly et al, 2012), such as microdroplet technology, which can detect one mutant KRAS gene among 200 000 wild-type KRAS genes in the plasma (Pekin et al, 2011). Thus, we think that the results of the study by Spindler et al (2013) should be interpreted with caution because the poor prognosis of patients with plasma KRAS mutation could only reflect the poor prognosis of patients with a high level of circulating tumour DNA, as suggested by some others studies (Lefebvre et al, 2010; Spindler et al, 2012). In contrast, the better prognosis could only reflect the low level of circulating tumour DNA that is not detectable by the ARMS assay for the KRAS mutation assay.

In conclusion, this promising work published by Spindler et al (2013) highlights the impact of circulating tumour DNA on the treatment response of metastatic colorectal cancer. Moreover, it strengthens the need for harmonising detection methods for KRAS mutations and to develop highly sensitive techniques for plasma testing. Thus, correlation of KRAS mutation in primary tumours, metastases and plasma during metastatic colorectal therapies still needs to be studied.

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