

study population twice, so these studies are arguably contributing more weight to the overall effect size than appropriate.

Despite the concerns raised, we acknowledge that the meta-analysis presented by Cong *et al* (2014) has drawn attention to the potential role of sedentary behaviour in colon and rectal cancer aetiology. Clearly further studies, using well-designed and tested measures of sedentary behaviour, are required in this field.

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*Correspondence: Dr BM Lynch; E-mail: brigid.lynn@bakeridi.edu.au
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Reply: Comment on 'Association of sedentary behaviour with colon and rectal cancer: a meta-analysis of observational studies'

Z Lu^{*1}, S Cao¹, Y Gan¹ and Y Cong¹

¹School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

We would like to thank Dr. Lynch and Boyle (2014) for their valuable comments and suggestions on our meta-analysis 'Association of sedentary behaviour with colon and rectal cancer: a meta-analysis of observational studies' (Cong *et al*, 2014). This meta-analysis made a timely and novel contribution to the literature about associations of sedentary behaviour on colon and rectal cancer risk. Although some imperfection may exist, they did not materially influence our result. Now, we are replying to the main comments mentioned by Lynch and Boyle.

Indeed, sedentary behaviour is distinctly different from occupational sedentarity and the lack of moderate- to vigorous-intensity physical activity. But in the included original studies, these exposures are difficult to be strictly differentiated. In our initial manuscript, we only focused on self-reported sedentary behaviours. On the basis of the suggestion of one of the reviewers, in order to avoid missing more relevant studies, we took into account the sedentary behaviour that is measured by job title-based response in the revised manuscript. Now, we did a subgroup analysis by types of assessment of sedentary behaviour, and the result showed that there was no substantial difference in the two types of measure of sedentary behaviour. For colon cancer, the pooled OR of sedentary behaviour measured by job title-based response was 1.39 (95% CI, 1.20–1.60, $I^2 = 63.7\%$), whereas the pooled OR of self-reported sedentary behaviour was 1.27 (95% CI, 1.18–1.36, $I^2 = 26.7\%$).

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The difference between them was insignificant (P for interaction = 0.289). For rectal cancer, the pooled OR of sedentary behaviour measured by job title-based response was 1.11 (95% CI, 1.03–1.20, $I^2 = 4.2\%$), whereas the pooled OR of self-reported sedentary behaviour was 1.01 (95% CI, 0.92–1.11, $I^2 = 19.7\%$). The difference between them was insignificant too (P for interaction = 0.156).

There are three studies that we included twice because the authors reported the risk estimates for two different measures of sedentary behaviour. Indeed, this may be contributing more (although not much more) weight to the overall effect size, but including only one of the two measures of sedentary behaviour is also inappropriate.

In summary, we appreciate most of Lynch and Boyle's comments and suggestions. Our meta-analysis indeed has some flaws, but these defects do not alter our main results and conclusions.

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*Correspondence: Professor Z Lu; E-mail: zuxunlu@yahoo.com
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Coexistence of KRAS mutation with mutant but not wild-type EGFR predicts response to tyrosine-kinase inhibitors in human lung cancer

A Choughule^{1,4}, R Sharma^{1,2,4}, V Trivedi^{1,2,4}, A Thavamani^{1,2}, V Noronha¹, A Joshi¹, S Desai³, P Chandrani², P Sundaram², S Utture¹, N Jambhekar³, S Gupta¹, J Aich^{*2}, K Prabhash^{*1} and A Dutt^{*2}

¹Department of Medical Oncology, Tata Memorial Hospital, Tata Memorial Center, Mumbai, India; ²Advanced Centre for Treatment, Research and Education in Cancer, Tata Memorial Center, Navi Mumbai, India and ³Department of Pathology, Tata Memorial Hospital, Tata Memorial Center, Mumbai, India

Sir,

EGFR and KRAS mutations occur mutually exclusively in NSCLC, suggesting functional redundancy (Kosaka *et al*, 2004; Pao *et al*, 2005;

Shigematsu *et al*, 2005; Tam *et al*, 2006). However, they predict contrasting response rates to tyrosine-kinase inhibitors (TKIs) – while EGFR mutation predicts longer progression-free survival rate (Lynch *et al*, 2004;

Table 1. EGFR and KRAS mutation co-occurrence in Indian NSCLC patients

Sample ID	EGFR mutation	KRAS mutation	Histology type	Gender	Smoking history	Response to gefitinib
LB-21	Exon-19 Del	G12C	Adenocarcinoma	Female	No	PR
LB-69	Exon-19 Del	G12C	Adenocarcinoma	Female	No	PR
LB-117	Exon-19 Del	G12C	Adenocarcinoma	Female	No	PR

Abbreviation: PR = partial response.

Mok *et al*, 2009; Fukuoka *et al*, 2011; Chougule *et al*, 2013), adverse prognosis is associated with patients harbouring KRAS mutations (Mao *et al*, 2010; Ihle *et al*, 2012). The recently reported co-occurrence of KRAS and EGFR activating mutations (Li *et al*, 2014) in 30 of 5125 patients raises questions about the relative values of EGFR and KRAS mutation status as predictors of outcome in NSCLC. This has obvious implications for routine KRAS testing in this disease, potentially precluding EGFR TKI therapy from some patients, similar to the current practice in colorectal cancer (Lievre *et al*, 2006).

EGFR mutations occur less frequently among Caucasians (10–15%) compared to East Asians (30–60%) (Lynch *et al*, 2004; Paez *et al*, 2004) in contrast to KRAS mutations for which the situation is opposite – Caucasians vs East Asians, 25–50% vs 5–15%, respectively (Mao *et al*, 2010; Roberts *et al*, 2010). We recently reported an intermediate frequency of EGFR mutations (23%) in a study involving 907 Indian NSCLC patients (Chougule *et al*, 2013). In a smaller study at our centre there was 74% response to TKI among patients with tumours having EGFR mutations compared to 5% in those with wild-type EGFR (Noronha *et al*, 2013). We performed directed sequencing of KRAS exons 2 and 3 in 86 patients from the same cohort and correlated its status with outcome after treatment with EGFR TKI (see Supplementary Table S1). There were 15 patients with KRAS G12C and 1 patient with KRAS G12V mutation for an overall mutation rate of 18.6%. Three of these 86 patients had coincident KRAS G12C and EGFR Exon-19 Del (E746-A750) mutations (Table 1), which were independently validated in each of the three samples by four orthogonal technologies (Sequenom Mass Array genotyping, Taqman Real Time PCR, Sanger Sequencing and SNaPshot PCR; see Supplementary Figure 1). All these three patients had partial response to EGFR TKI. However, only 1 of the remaining 13 patients with KRAS mutation had partial response and his tumour had wild-type EGFR with unknown copy number. This is consistent with previous studies: response to EGFR TKI in one of five patients harbouring KRAS mutation with unknown EGFR copy number or mutation status (Zhu *et al*, 2008); 1 response in 20 KRAS mutant patients who also harboured EGFR amplification but not EGFR mutation (Gumerlock *et al*, 2005); and response to gefitinib in three of five patients with coincident EGFR and KRAS mutations (Benesova *et al*, 2010). Furthermore, it has been shown that when KRAS and EGFR mutations are coincident in the same tumour, the genetic lesion in the latter is almost exclusively in exon-19, with virtually no occurrence of exon-21 abnormalities (Li *et al*, 2014). This was also true in all three cases in our series with coincident EGFR and KRAS mutations. Of note, mutations in exon-19 have been shown to predict a higher response to EGFR TKI than those in exon-21 (Mitsudomi *et al*, 2005).

In summary, these data suggest that NSCLC patients with KRAS mutations are unlikely to respond to EGFR TKI therapy in the absence of coincident EGFR alterations. Therefore additional KRAS molecular testing may not add predictive value in selecting patients for EGFR TKI therapy and cannot be routinely recommended.

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*Correspondence: Dr J Aich; E-mail: jyoti.aich@gmail.com or Dr K Prabhaskar;

E-mail: kprabhaskar1@gmail.com or Dr A Dutt; E-mail: adutt@actrec.gov.in

†These authors contributed equally to this work.

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