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.

REFERENCES

Ainsworth BE, Richardson MT, Jacobs Jr DR, Leon AS, Sternfield B (1999) Accuracy of recall of occupational physical activity by questionnaire. *J Clin Epidemiol* **52**: 219–227.

Campbell PT, Patel AV, Newton CC, Jacobs EJ, Gapstur SM (2013) Associations of recreational physical activity and leisure time spent sitting with colorectal cancer survival. *J Clin Oncol* **31**: 876–885.

Colbert LH, Hartman TJ, Malila N, Limburg PJ, Pietinen P, Virtamo J, Taylor PR, Albanes D (2001) Physical activity in relation to cancer of the colon and rectum in a cohort of male smokers. *Cancer Epidemiol Biomarkers Prev* **10**: 265–268.

Cong YJ, Gan Y, Sun HL, Deng J, Cao SY, Xu X, Lu ZX (2014) Association of sedentary behaviour with colon and rectal cancer: a meta-analysis of observational studies. *Br J Cancer* **110**: 817–826.

Fraser G, Pearce N (1993) Occupational physical activity and risk of cancer of the colon and rectum in New Zealand males. *Cancer Causes Control* **4**: 45–50.

Garabrant DH, Peters JM, Mack TM, Bernstein L (1984) Job activity and colon cancer risk. *Am J Epidemiol* **119**: 1005–1014.

Howard RA, Freedman DM, Park Y, Hollenbeck A, Schatzkin A, Leitzmann MF (2008) Physical activity, sedentary behaviour, and the risk of colon and rectal cancer in the NIH-AARP Diet and Health Study. *Cancer Causes Control* **19**: 939–953.

LaPorte RE, Montoye HJ, Caspersen CJ (1985) Assessment of physical activity in epidemiologic research: problems and prospects. *Public Health Rep* **100**: 131–146.

Moradi T, Gridley G, Bjork J, Dosemeci M, Ji BT, Berkel HJ, Lemeshow S (2008) Occupational physical activity and risk for cancer of the colon and rectum in Sweden among men and women by anatomic subsite. *Eur J Cancer Prev* **17**: 201–208.

Thune I, Lund E (1996) Physical activity and risk of colorectal cancer in men and women. *Br J Cancer* **73**: 1134–1140.

Weiderpass E, Vainio H, Kauppinen T, Vasama-Neuvonen K, Partanen T, Pukkala E (2003) Occupational exposures and gastrointestinal cancers among Finnish women. *J Occup Environ Med* **45**: 305–315.

Yates T, Wilmot EG, Davies MJ, Gorely T, Edwardson C, Biddle S, Khunti K (2011) Sedentary behaviour: what's in a definition? *Am J Prev Med* **40**: e33–e34.

*Correspondence: Dr BM Lynch; E-mail: brigid.lynch@bakeridi.edu.au
Published online 25 February 2014

BJC

British Journal of Cancer (2014) 111, 2203 | doi:10.1038/bjc.2014.107

Reply: Comment on 'Association of sedentary behaviour with colon and rectal cancer: a meta-analysis of observational studies'

Z Lu*[,1], S Cao[1], Y Gan[1] and Y Cong[1]

[1]*School 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 sedentariness 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, $I^2 = 26.7\%$). 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.

REFERENCES

Cong YJ, Gan Y, Sun HL, Deng J, Cao SY, Xu X, Lu ZX (2014) Association of sedentary behaviour with colon and rectal cancer: a meta-analysis of observational studies. *Br J Cancer* **110**: 817–826.

Lynch BM, Boyle T (2014) Distinguishing sedentary from inactive: implications for meta-analyses. *Br J Cancer* **111**: 2202–2203.

*Correspondence: Professor Z Lu; E-mail: zuxunlu @yahoo.com
Published online 25 February 2014

BJC

British Journal of Cancer (2014) 111, 2203–2204 | doi:10.1038/bjc.2014.401

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 Noronha[1], A Joshi[1], S Desai[3], P Chandrani[2], P Sundaram[2], S Utture[1], N Jambhekar[3], S Gupta[1], J Aich*[,2], K Prabhash*[,1] and A Dutt*[,2]

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

REFERENCES

Benesova L, Minarik M, Jancarikova D, Belsanova B, Pesek M (2010) Multiplicity of EGFR and KRAS mutations in non-small cell lung cancer (NSCLC) patients treated with tyrosine kinase inhibitors. *Anticancer Res* **30**(5): 1667–1671.

Chougule A, Prabhash K, Noronha V, Joshi A, Thavamani A, Chandrani P, Upadhyay P, Utture S, Desai S, Jambhekar N, Dutt A (2013) Frequency of EGFR mutations in 907 lung adenocarcioma patients of Indian ethnicity. *PLoS One* **8**(10): e76164.

Fukuoka M, Wu YL, Thongprasert S, Sunpaweravong P, Leong SS, Sriuranpong V, Chao TY, Nakagawa K, Chu DT, Saijo N, Duffield EL, Rukazenkov Y, Speake G, Jiang H, Armour AA, To KF, Yang JC, Mok TS (2011) Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol* **29**(21): 2866–2874.

Gumerlock PH, Holland WS, Chen H, Franklin WA, Hirsch FR, Mack PC, Davies AM, McCoy J, West HJ, Gandara DR (2005) Mutational analysis of K-RAS and EGFR implicates KRAS as a resistance marker in the Southwest Oncology Group (SWOG) trial S0126 of bronchioalveolar carcinoma (BAC) patients (pts) treated with gefitinib. *Proc Am Soc Clin Oncol* **23**(Suppl 623s): abstr 7008.

Ihle NT, Byers LA, Kim ES, Saintigny P, Lee JJ, Blumenschein GR, Tsao A, Liu S, Larsen JE, Wang J, Diao L, Coombes KR, Chen L, Zhang S, Abdelmelek MF, Tang X, Papadimitrakopoulou V, Minna JD, Lippman SM, Hong WK, Herbst RS, Wistuba II, Heymach JV, Powis G (2012) Effect of KRAS oncogene substitutions on protein behavior: implications for signaling and clinical outcome. *J Natl Cancer Inst* **104**(3): 228–239.

Kosaka T, Yatabe Y, Endoh H, Kuwano H, Takahashi T, Mitsudomi T (2004) Mutations of the epidermal growth factor receptor gene in lung cancer: biological and clinical implications. *Cancer Res* **64**(24): 8919–8923.

Li S, Li L, Zhu Y, Huang C, Qin Y, Liu H, Ren-Heidenreich L, Shi B, Ren H, Chu X, Kang J, Wang W, Xu J, Tang K, Yang H, Zheng Y, He J, Yu G, Liang N (2014) Coexistence of EGFR with KRAS, or BRAF, or PIK3CA somatic mutations in lung cancer: a comprehensive mutation profiling from 5125 Chinese cohorts. *Br J Cancer* **110**(11): 2812–2820.

Lievre A, Bachet JB, Le Corre D, Boige V, Landi B, Emile JF, Côté JF, Tomasic G, Penna C, Ducreux M, Rougier P, Penault-Llorca F, Laurent-Puig P (2006) KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res* **66**(8): 3992–3995.

Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J, Haber DA (2004) Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* **350**(21): 2129–2139.

Mao C, Qiu LX, Liao RY, Du FB, Ding H, Yang WC, Li J, Chen Q (2010) KRAS mutations and resistance to EGFR-TKIs treatment in patients with non-small cell lung cancer: a meta-analysis of 22 studies. *Lung Cancer* **69**(3): 272–278.

Mitsudomi T, Kosaka T, Endoh H, Horio Y, Hida T, Mori S, Li J, Chen Q (2005) Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. *J Clin Oncol* **23**(11): 2513–2520.

Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M (2009) Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* **361**(10): 947–957.

Noronha V, Prabhash K, Thavamani A, Chougule A, Purandare N, Joshi A, Sharma R, Desai S, Jambekar N, Dutt A, Mulherkar R (2013) EGFR mutations in Indian lung cancer patients: clinical correlation and outcome to EGFR targeted therapy. *PLoS One* **8**(4): e61561.

Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE, Meyerson M (2004) EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* **304**(5676): 1497–1500.

Pao W, Wang TY, Riely GJ, Miller VA, Pan Q, Ladanyi M, Zakowski MF, Heelan RT, Kris MG, Varmus HE (2005) KRAS mutations and primary resistance of lung adenocarcinomas to gefitinib or erlotinib. *PLoS Med* **2**(1): e17.

Roberts PJ, Stinchcombe TE, Der CJ, Socinski MA (2010) Personalized medicine in non-small-cell lung cancer: is KRAS a useful marker in selecting patients for epidermal growth factor receptor-targeted therapy? *J Clin Oncol* **28**(31): 4769–4777.

Shigematsu H, Lin L, Takahashi T, Nomura M, Suzuki M, Wistuba II, Fong KM, Lee H, Toyooka S, Shimizu N, Fujisawa T, Feng Z, Roth JA, Herz J, Minna JD, Gazdar AF (2005) Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst* **97**(5): 339–346.

Tam IY, Chung LP, Suen WS, Wang E, Wong MC, Ho KK, Lam WK, Chiu SW, Girard L, Minna JD, Gazdar AF, Wong MP (2006) Distinct epidermal growth factor receptor and KRAS mutation patterns in non-small cell lung cancer patients with different tobacco exposure and clinicopathologic features. *Clin Cancer Res* **12**(5): 1647–1653.

Zhu CQ, da Cunha Santos G, Ding K, Sakurada A, Cutz JC, Liu N, Zhang T, Marrano P, Whitehead M, Squire JA, Kamel-Reid S, Seymour L, Shepherd FA, Tsao MS (2008) Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. *J Clin Oncol* **26**(26): 4268–4275.

*Correspondence: Dr J Aich; E-mail: jyoti.aich@gmail.com or Dr K Prabhash; E-mail: kprabhash1@gmail.com or Dr A Dutt; E-mail: adutt@actrec.gov.in

[4]These authors contributed equally to this work.

Published online 12 August 2014