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Reply to 'Comment on: The NQO1 polymorphism C609T (Pro187Ser) and cancer susceptibility: a comprehensive meta-analysis'

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Sir,

We have strictly followed the published general guidelines for conducting meta-analyses (Stroup *et al*, 2000; Minelli *et al*, 2009). Therefore we tested for deviations from HWE and reported in our paper the deviation of five studies from HWE. Deviation from HWE may imply genotyping error and/or possible heterogeneity in the control population. Most of the excluded studies strongly violated HWE with *P*-values = 0. Nevertheless, when the five studies were included in the meta-analysis the association remained statistically significant with almost unaltered odds ratios. For example, for the TT *vs* CC model OR = 1.17 (1.06–1.30), $P = 0.002$, compared to the reported results with the exclusion of the five studies, OR = 1.18 (1.07–1.31), $P = 0.002$. This is not unexpected given the large number of studies included and the fact that the majority of studies were in compliance with the HWE principle. This confirms that no bias has been introduced by the exclusion of the five studies and that the concluded positive association between total cancer risk and the investigated polymorphism is unaffected.

The distinction between the source of controls was not made unambiguously in all published papers. Therefore, we avoided stratification according to the source of controls. In addition, we believe that such stratification is irrelevant within the context of our meta-analysis and that there is no difference in the genotypic distribution between hospital-based and population-based controls since it is assumed that the control subjects in all studies were not diagnosed with any type of cancer or any other condition commonly associated with the studied polymorphism.

Finally, we believe that it is unlikely that the inadvertently missed single-case sample had an impact on the results and conclusions of the meta-analysis that included 21178 case samples.

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Distinguishing sedentary from inactive: implications for meta-analyses

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We read with great interest the meta-analysis by Cong *et al* (2014) recently published in *British Journal of Cancer*. As the authors acknowledge, sedentary behaviour is distinct from the lack of moderate- to vigorous-intensity physical activity. As the first quantitative review of the studies examining associations of sedentary behaviour on colon and rectal cancer risk, this article makes a timely and novel contribution to the literature. However, we are concerned that the combined risk estimates generated by this meta-analysis may not accurately reflect the effect that can be attributed to sedentary behaviour.

Many of the risk estimates included in the meta-analysis are from studies that investigated the association between occupational physical activity and the risk of colon and/or rectal cancers. As noted by Yates *et al* (2011), the ordinal scales commonly used to assess occupational physical activity (e.g., 'sedentary', 'moderate', 'high') are not necessarily ordinal scales of sedentary behaviour. As high levels of sedentary behaviour can co-exist with high levels of physical activity, even within specific occupations, using these estimates of occupational physical activity to infer sedentary behaviour is likely to introduce substantial misclassification bias.

A related issue is the inclusion of studies that have classified sedentary behaviour based on job title. While we do not believe it is necessarily wrong to include estimates of sedentary behaviour that are job title based, it is important to note that this method does not take into account within-job variation, seasonal changes or changes in job requirements over time (LaPorte *et al*, 1985), and may not reflect the actual activities performed on the job (Ainsworth *et al*, 1999). We would recommend that in future meta-analyses and reviews, these studies be given a lower exposure assessment quality rating than studies using self-reported or objectively assessed measures of sedentary behaviour. In addition, we suggest that subgroup analyses are conducted to investigate whether the results of studies relying on job title-based measures of sedentary behaviour differ from the results of studies with self-reported or objectively assessed measures of sedentary behaviour.

Another issue that arises when using ordinal scales of occupational physical activity (job title-based or self-reported) in a sedentary behaviour context is the selection of the appropriate referent category. The most suitable referent group to compare jobs with high amounts of sedentary behaviour with are jobs that involve 'mostly standing' or 'light' activity. Within the meta-analysis performed by Cong *et al* (2014), there are several instances where the authors selected the most physically active category as the referent group (Garabrant *et al*, 1984; Fraser and Pearce, 1993; Weiderpass *et al*, 2003; Moradi *et al*, 2008). The relative risks generated by comparing the sedentary category with the most physically active will not solely reflect the effect of sedentary behaviour on colorectal cancer risk; part of the risk estimate will be attributed to the (inverse) of the risk reduction associated with physical activity. A similar error was made with the inclusion of data from two studies that compared recreational sedentary behaviour with recreational physical activity (Thune and Lund, 1996; Colbert *et al*, 2001).

There are two final points that we would like to raise. First, the risk estimates included in the meta-analysis from the Campbell *et al* (2013) study pertain to colorectal cancer-specific survival rather than colorectal cancer risk. Second, there are three studies for which the authors have included risk estimates for two different measures of sedentary behaviour (e.g., recreational and occupational sedentary behaviour) in the primary meta-analysis (Thune and Lund, 1996; Colbert *et al*, 2001; Howard *et al*, 2008). This is effectively including the same

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

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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.

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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

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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;