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

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Sir,

The aim of the performed meta-analysis was mainly to investigate the association between the overall cancer risk and the *NQO1* C609T polymorphism in the worldwide population as well as in individual ethnic groups, given the biological plausibility of combining several different cancer sites in the light of the common background implied by the known functions of the investigated enzyme. Most notably, our meta-analysis demonstrated a statistically significant association in the worldwide and Caucasian populations, as indicated by the resulting *P*-values. Power analysis was not published for most of the individual studies, and therefore it was not reported in our meta-analysis for each individual study. The main purpose of conducting the present meta-analysis was to overcome the expected low power in most of the individual studies due to the small sample sizes, and at least improve the power of detecting association by combining the large number of studies. The calculated power for our present meta-analysis was 97% for the worldwide population analysis and 98% for the Caucasian subgroup analysis ($\alpha = 0.05$). Calculations were performed using the genetic power calculator developed by Purcell *et al* (2003). Therefore, the conclusions of the meta-analysis are further supported by the obtained high power, which was not unexpected given the large total number of samples, the significant resulting odds ratios, and the low *P*-values. The power obtained far exceeds the standard, and rather arbitrary, value of 80% with respect to the worldwide and Caucasian population, which leaves no possibility of a false-positive association. Concerning the tumour site analysis, we had noted in the article that the results should be approached with caution due to the small sample sizes available, and we highlighted the need for more studies investigating individual cancer sites and involving less common ethnic groups in the conclusion. The main conclusion from the meta-analysis performed involved the total cancer risk combining all tumour sites.

It is noteworthy that *post hoc* power analysis is controversial and often misinterpreted (Hoenig and Heisey, 2001). The common well-accepted usage for power is in prospectively estimating a sufficient sample size to detect an association when it is present in order to avoid type II error and false-negative associations.

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 21 178 case samples.

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Need for clarification of data in a recent meta-analysis on the association of *NQO1* C609T polymorphism with cancer risk

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We read with great interest the recent paper by Lajin and Alachkar (2013). The authors performed a comprehensive meta-analysis of 92 case–control studies involving 21 178 cancer cases and 25 157 controls to examine the association between *NQO1* C609T polymorphism and cancer susceptibility. Their comprehensive meta-analysis results suggest that *NQO1* C609T polymorphism is an important genetic factor in the overall risk for developing cancer, especially in Caucasian populations. It is an interesting study. Nevertheless, we would like to raise several concerns related to this article.

First, sensitivity analysis may need to be routinely performed by excluding and including the Hardy–Weinberg equilibrium (HWE)-violating studies in meta-analyses of genetic association studies, which is a good approach to heterogeneity (Mao *et al*, 2010). We also assessed deviation from HWE in controls for all the included studies, and the results demonstrated that most genotype distributions for the control group were well goodness-of-fit except for five studies. However, the authors only performed the meta-regression analysis to identify three possible sources of heterogeneity including ethnicity, tumour site, and minor allele frequency (MAF). We would recommend that in their meta-analyses, the authors should conduct the meta-regression analysis including HWE, not only excluded these five studies deviated from HWE. Therefore, we believe that the bias would be introduced into the results of the meta-analysis due to this shortage.

Second, in the meta-analysis, the authors have retrieved data on the source of control groups (hospital- or population-based controls), but the definitions for the population-based study and hospital-based study were not clear in this meta-analysis. This point greatly influenced the results of this meta-analysis. For example, if the authors defined the population-based study as controls from healthy population, and the hospital-based study as controls from patients, we could clearly ascertain that at least the report by Zhang *et al* (2003) was not a population-based study. Furthermore, the authors should perform a stratified analysis by source of control groups.

Finally, the data reported by Lajin and Alachkar (2013) do not seem in line with the data provided by Malik *et al* (2011) in their original publication. The numbers reported by Lajin and Alachkar (2013) for CC, CT, and TT, in cases and controls, respectively, are 51–38–18 and 112–68–15. Interestingly enough, after carefully studying the data presented by Malik *et al* (2011), the frequencies that we have retrieved on the 108 cases and 195 controls were 51–39–18 and 112–68–15, respectively. Therefore, this similar error may exist in other included studies in the meta-analysis. It would be valuable if the authors could provide a more careful checking for genotype data in previously published studies.

In conclusion, the above comments may reveal that the association between the *NQO1* C609T polymorphism and cancer susceptibility was conflicting. We believe that this remark will contribute to further, more accurate elaboration and substantiation of the original results presented by Lajin and Alachkar (2013).

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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