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EDITORIAL

Letter regarding Zhu et al. entitled "Assessment of the association between XRCC1 Arg399Gln polymorphism and glioma susceptibility"

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To the Editor,

Recently, we read with great interest the article "Assessment of the association between XRCC1 Arg399Gln polymorphism and glioma susceptibility" published online in November 21, 2013 of *Tumor Biology* [1], which has reached important conclusions about the relationship between Arg399Gln polymorphism and glioma risk. Through quantitative analysis, this meta-analysis suggested that XRCC1 Arg399Gln polymorphism decreased the risk of glioma in the whole population (odds ratio (OR)$_{GG\ vs.\ AG\ +\ AA}$=0.90, 95 % CI=0.84–0.97, $P_{heterogeneity}$=0.020; OR$_{allele\ G\ vs.\ allele\ A}$=0.96, 95 % CI=0.91–1.00, $P_{heterogeneity}$=0.110), especially in Asians (OR$_{GG\ vs.\ AG\ +\ AA}$=0.84, 95 % CI=0.72–0.97, $P_{heterogeneity}$=0.971; OR$_{allele\ G\ vs.\ allele\ A}$=0.91, 95 % CI=0.83–1.00, $P_{heterogeneity}$=0.993).

Nevertheless, there are some comments we would like to raise. First, several recent published meta-analyses [2–6] had estimated the association between Arg399Gln polymorphism and glioma risk, basically coinciding with the conclusion that variant Gln (A) allele of Arg399Gln polymorphism (rs25487) may contribute to the susceptibility of glioma in Asians [3–6]. In contrast, the meta-analysis performed by Zhu et al. [1] indicated a decreased susceptibility in association with the GG genotype and allele G of the Arg399Gln polymorphism in Asians. The major reason for the discrepancy between the previous meta-analyses and the study by Zhu et al. is the different models being tested. Obviously, rs25487, but not rs25478 that was indicated in the study by Zhu et al. [1], is the SNP known as Arg399Gln that was investigated in these meta-analyses. The variant allele A encodes the Gln amino acid, while the wild allele G encodes the Arg amino acid. So the definition of GG or AA in the genetic model, accurate genotype frequency of case/control should be clarified or listed in the meta-analysis performed by Zhu et al. [1]. Actually, the additive model for allele G versus allele A in the meta-analysis by Zhu et al. [1] is equal to Arg versus Gln. Therefore, the conclusion drawn by Zhu et al. [1], to some extent, seems the same as that of the aforementioned meta-analyses [3–6] rather than the opposite.

Second, researchers should find out the overlapping data in the included studies during a meta-analysis. And it might lead to duplicate counting of subjects and overestimation of intervention effects in meta-analyses [7–9] because subjects from the same trials are reanalyzed repeatedly, without disclosure, in different studies. Therefore, from this sense, the validity of meta-analyses done without looking into this problem is questionable [9]. After carefully inspecting the detailed information on all eligible literatures, we found that the study by McKean-Cowdin et al. [10] combined the genetic data for XRCC1 polymorphisms from four centers (NCI, MDA, UCSF, and NIOSH) and contained partial overlapping data with the study by Rajaraman et al. (NCI) [11], Liu et al. (MDA) [12], and Felini et al. (UCSF) [13], respectively. According to the inclusion criteria that only the largest study should be included in the final analysis if studies had the same or overlapping data, the estimation regarding Arg399Gln polymorphism and glioma susceptibility should contain the studies by Rajaraman et al. [11], Liu et al. [12], and Felini et al.

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[13], but not the study by McKean-Cowdin et al. [10]. Although the effects of overlapping data on the results of quantitative analysis had been realized in the meta-analysis of Zhang et al., it was not be recognized by Zhu et al. [1] and other groups when performing the meta-analyses.

Third, the study by Liu et al. [12] should not be excluded for providing the insufficient genotyping data because the numbers in cases and controls could be calculated by the minor allele frequency (MAF). And the separate data for Arg/Arg, Arg/Gln, and Gln/Gln in cases and controls, respectively, are 149–162–62 and 169–145–50. Furthermore, the data of sample sizes reported by Zhu et al. [1] for the studies by Kiuru et al. [14] and Liu et al. [15] also do not seem in line with the data provided in their original publications. The numbers of cases and controls reported by Zhu et al. [1] for these two studies, respectively, are 699–519 and 79–79. After closely examining the original data, we found that the numbers reported by Kiuru et al. [14] and Liu et al. [15] for cases and controls should be 699–1,549 and 89–89, respectively. In addition, Yosunkaya et al. [16] concluded that XRCC1 Arg399Gln polymorphism was a significant risk factor, and 399Gln (G) allele carried a 3.5 times greater risk for glioma ($OR_{\text{allele G vs. allele A}}=0.29$, 95 % CI=0.203–0.416). However, if G allele vs. A allele correspond to Arg vs. Gln, the original result of the study by Yosunkaya et al. [16] is not uniform with that shown in the forest plot by Zhu et al. ($OR_{\text{allele G vs. allele A}}=0.58$, 95 % CI=0.44–0.77), suggesting that the data might be inaccurate during the process of data extraction. Hence, the ongoing uncertainty still exists, and the conclusion by Zhu et al. [1] was not entirely credible.

In conclusion, we are convinced that the Gln allele of Arg399Gln polymorphism was significantly associated with the increased risk of glioma among Asians ($OR_{\text{Gln vs. Arg}}=1.33$, 95 % CI=1.18–1.51). And the conclusion by Zhu et al. [1] that appears paradoxical, in fact, was consistent with that of the aforementioned meta-analyses. What's more, two recent published reports [17, 18] agreed on the above conclusions. However, considering the limited number of studies, in the future, more studies on race-specific populations are needed so as to validate the present results in larger sets of case–control studies.

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Conflicts of interest None

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