

LETTER to the EDITOR

Gestational Diabetes Mellitus and Subsequent Cancer Risk: Shared Risk Factors, Causality or Confounding?*Asian Pac J Cancer Prev*, **15** (24), 11001**Dear Editor**

A number of epidemiological studies have focused on the possible association between gestational diabetes mellitus (GDM) and subsequent cancer risk, attempting to shed light on the role of pregnancy in cancer etiology (Cnattingius et al., 2005; Sella et al., 2011; Brasky et al., 2013; Tong et al., 2014). A recent report by Tong and colleagues updated our knowledge on this issue with summarized results from a systematic review, which suggested contributions from GDM to subsequent risk of certain cancers and highlighted the needs for further investigations (Tong et al., 2014).

The explanation on the relationship between GDM and subsequent cancer risk seems not straightforward and remains under discussion. It is possible that GDM does affect subsequent cancer risk via some biological mechanisms. Shared risk factors may be an alternative explanation. On the other hand, because GDM may be associated with many risk factors of cancers (Yang et al., 2013), including both intrinsic (e.g. hormone levels and genetic background influencing more than one phenotypes) and extrinsic exposures, there would be a great risk of confounding if potential confounders have not been adequately controlled for.

The validity of a systematic review and/or meta-analysis can be affected by that in the primary studies, which is based on the analogy “garbage in, garbage out” (Yu and Tse, 2013). Thus, assessing the validity of primary studies would be an essential part of a systematic review. However, the systematic review reported by Tong et al was lack of such important information. Readers may want to know how efforts had been made to control for potential confounding effects. Potential selection bias, such as incomplete follow-up in cohort studies and low response rates in case-control studies, might have affected the representativeness of the population, and consequently, affected the validity of the pooled results in the systematic review. Thus, the possibility of residual confounding effects and selection bias from the primary studies could not be ruled out.

Exposure misclassification is another particular methodological issue which needs to be discussed hereby. Several studies included in this systematic review used self-reported estimates instead of objective clinical diagnosis based on biochemical testing. If these studies had assessed the agreement of self-reported GDM and biochemical diagnosis and how the agreement was like according to (stratified by) outcome status, there results

would have been more convincing. We also recommend including stratified analyses by cancer sub-sites and histological types in future studies because of the possible etiological differences in terms of directions and strengths of their associations with GDM. It would certainly require even larger sample sizes.

In summary, convincing evidence regarding the association between GDM and subsequent cancer risk remains necessary. The usefulness of GDM as a predictor for subsequent cancer risk and the underlying mechanism still need to be clarified.

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