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Letter to the Editor

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Reply to the letter to the editor 'The Role of Nutrition and Genetics in Thyroid Cancer Risk'

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We read the letter to the editor regarding 'The role of nutrition and genetics in thyroid cancer risk', which discusses some points of our study 'Association of dietary manganese intake and the *IL1R1* rs3917225 polymorphism with thyroid cancer (TC) risk: a prospective cohort study in Korea'. We sincerely appreciate that your team shares a similar interest in this important research area. You raise valuable points that are crucial for understanding the implications of our findings and warrant further discussion.

To the best of our knowledge, environmental factors, such as ionising radiation and a history of benign thyroid nodules, may influence TC. We conducted this study at the Korean National Cancer Center, where medical information was collected, including general past medical history, clinical tests, physical examinations, cancer screening and biological specimens. As a result, several environmental exposures such as ionising radiation were not evaluated in our study, which could potentially introduce bias to the observed relationship. Thus, we consider it as a limitation in the manuscript.

In our study, information on the participants' diets in the year preceding the interview was collected by using a semi-quantitative FFQ with 106 food items, including nine categories and three categories regarding the frequency of food consumption and portion size, respectively. The assessment of the validity and reliability of the semi-quantitative FFQ has been reported previously. Since TC has a long latency period, we collected information on diet at baseline to accurately assess the causal relationship between dietary exposure and TC development. This approach is common in nutritional epidemiology, as seen in previous studies such as Park et al.'s investigation of diet-dependent acid load and breast cancer risk[(1)] and Jun et al.'s study focussed on fibre and gastrointestinal track cancer[(2)]. Nevertheless, we acknowledge the possibility of dietary variation during the follow-up period, and we consider this a limitation of our research.

Although we have some limitations, our study used a prospective cohort design with a high-quality database that was linked to the national cancer registry and medical records to ascertain incident cancer cases. Additionally, a validated FFQ, specifically designed for the Korean population, was used to collect information on nutrient intake, ensuring that the eating habits of the study population were accurately represented in our study. Therefore, our study contributes meaningful evidence regarding the potential preventive role of Mn in TC.

The association of the *IL1R1* rs3917225 polymorphism with thyroid cancer risk

Inflammation has been widely recognised to be a contributor in the carcinogenesis and its involvement in TC development has been confirmed. *IL1R1* utilises three alternative promoters, producing distinct transcripts. The promoter region of *IL1R1* is notably polymorphic, potentially influencing expression levels across various tissues[(3)]. The SNP in the promoter region of *IL1R1* gene may have an impact on the affinity of *IL1* to *IL1R1* and thereby affecting inflammation[(4)]. A few studies were conducted to analyse the association between rs3917225 and TC. Although the significance of rs3917225 is decreased with additional adjustment for age and sex, a previous study suggests the correlation between rs3917225 and TC in Chinese Han people[(5)]. In contrast, rs3917225 was not associated with the location of papillary thyroid carcinoma, whereas another promoter SNP rs2192752 has an association with papillary thyroid carcinoma in Korean population[(3)]. Notably, rs3917225 demonstrated the potential to lower TC risk under the dominant model in our study. Possible mechanisms may be proposed. A previous study supposes that this variant may impact on recruitment of RNA polymerase for *IL1R1* leading to disturbing the initiation of transcription and subsequent signal transduction pathways[(5)]. Additionally, this genetic variant might affect the affinity of *IL1* to *IL1R1*, hence blocking the upregulation of inflammation[(4)]. However, the mechanism remains unclear; similar to a previous study[(5)], our research indicates that the impact of this variant cannot be entirely overlooked. Thus, further research with a larger sample size of TC is required to elucidate the possible mechanisms underlying this association.

Furthermore, the interaction between gene and diet may explain the wide differences in cancer susceptibility across populations[(6)]. Dietary Mn has been emphasised to have an association with circulating inflammation markers and the NF-$\kappa\beta$ pathway[(7,8)]. Thus, we

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hypothesised an interaction between rs3917225 and Mn and its potential impact on TC development. Importantly, our study found that the protective effect of Mn against TC risk depends on an individual's genetic background. Specifically, a higher Mn intake tended to emerge as a beneficial effect against TC in minor allele carriers. The connection between Mn and inflammation may serve as a potential mechanism underlying the interaction between rs3917225 and Mn, as highlighted in previous studies. First, a previous study documented that participants with an increased Mn intake showed lower levels of interleukin 6 and hs-CRP[7]. Second, Mn may contribute to the production of inflammatory biomarkers as presented by concentrations of IL-1β, IL-8, IL-6 and NF-$\kappa\beta$ when the intake level is slightly above nutritional sufficiency[8]. Third, Mn was identified as a dominant trace metal in relation to increased IL-1β levels in another previous study[9]. We also provided possible mechanisms that may be proposed for the link between Mn and IL-1β in the manuscript. First, studies focus on the mechanisms of Mn indicate that upon entering cells, it has the potential to be sequestered within mitochondria leading to calcium ion transport disruption, mitochondrial dysfunction and an imbalance in intracellular redox status[9]. Second, Mn may influence danger-associated molecular patterns and stimulate IL-1β production[9]. Third, Mn intake was associated with DNA methylation of NF-$\kappa\beta$-regulating genes and thus, contributing to interleukin production[8].

Our study is the first to explore the interaction of the rs3917225 and Mn on TC risk. This is the main finding of our study. We want to emphasise that the effect of Mn on TC depends on an individual's genetic background. The biological mechanism underlying this interaction remains unclear; however, we emphasise the importance of considering each individual's genetic background when assessing the cancer-preventive role of Mn. Due to the limitations of our study, further research with a larger number of TC cases is needed to address this concern.

The association of the dietary manganese intake with thyroid cancer risk

To date, the effect of Mn on autoimmune thyroid diseases and thyroid tumours has been controversial. Our study aimed to clarify this association, finding evidence for a protective role of Mn against TC, while emphasising the importance of an appropriate level of Mn consumption. For clarity, we would like to reiterate some points from our manuscript:

'To our knowledge, this is the first epidemiological study focusing on the relationship of dietary Mn intake with TC. It indicates that an appropriate level of Mn consumption could potentially lead to a reduced TC risk'

'While adequate intake of Mn has several beneficial effects including lowering oxidative stress[20], the high concentrations could potentially be toxic[39] whereas its deficiency may cause inflammation and endothelial dysfunction[19]'.

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The authors declare that they have no conflicts of interests.

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