Incidence of PPGL according to altitude – Calendar time is of the essence

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We recently read the article by Leung *et al.* (1) on the incidence of pheochromocytoma and paraganglioma (PPGL) with great enthusiasm. However, we have some concerns regarding the recent speculations on the relationship between the incidence of PPGL and the ‘modifiable’ risk factor of altitude in the correspondence between Patel and Mihai (2) and Leung *et al.* (3). In the first letter, Patel and Mihai laid out the evidence for the pseudo-hypoxia model as a cause of PPGL (4) and speculate on a possible association between altitude, hypoxia, and PPGL. In their reply, Leung *et al.* report the results of a meta-regression analysis to support the theory.

Unfortunately, Leung *et al.* do not provide any detail on how papers in their meta-regression were selected, while a number of other studies were not included (5, 6, 7, 8, 9, 10, 11). We therefore searched for all papers presenting the incidence of PPGL in a defined geographic location. We screened the identified references and included 14 relevant papers. Taking all these studies into account and collecting annual incidence rates rather than study averages, we redid the meta-regression analysis on the incidence of PPGL and altitude. The search strategy, study data, and code are available on <https://github.com/andreasebbehøj/2021-EJE-letter-PPGL-altitude-and-time>. In our analysis, altitude was still a predictor of PPGL incidence (Fig. 1A). However, the regression line fits the data poorly ($R^2=23.0\%$), and there is considerable heterogeneity between estimates ($I^2=93.8\%$). Therefore, a meta-regression of these heterogeneous studies should be interpreted with caution.

It is surprising that Leung *et al.* do not find an association between time and incidence rate. This is in contrast with a combined systematic review and nationwide study by Berends *et al.* (12), who showed an increasing incidence of PPGL in both previously published studies and in the Netherlands. We find it worth noting

that the study by Kim *et al.* (13) is the largest study in Leung *et al.*’s meta-analysis but seems to be an outlier compared to other recent studies (Fig. 1B). Kim *et al.* (13) base their incidence rates on an unvalidated registry-based algorithm, which combine diagnosis codes, surgery codes, and biochemical tests. Having previously validated another PPGL algorithm, we have no doubt that the combination of PPGL-related surgery and diagnosis codes will have a positive predictive value close to 100% but will also likely lead to an underreporting of PPGL patients by 20–40% (14). Underreporting does not invalidate Kim *et al.*’s clinical findings *per se*, but it is far from an ideal study design to determine the incidence of PPGL. Having said that, Kim *et al.*’s data do actually also show an increase in the incidence of PPGL over time.

Based on the included studies, we find it evident that the incidence of diagnosed PPGL is indeed increasing over time. The fact that Leung *et al.*’s meta-regression analysis does not find any association between incidence and year of publication raises the question if the year of publication is a good measure when studies often cover one or several decades. Indeed, if redoing the meta-regression with annual incidence rates, the time trend is clear, though estimates vary considerably ($R^2=47.0\%$ and $I^2=90.9\%$, Fig. 1B). If excluding Kim 2020, the association with time becomes even clearer ($R^2=70.3\%$ and $I^2=81.5\%$), while the association with altitude remains poor ($R^2=21.6\%$ and $I^2=92.3\%$).

In conclusion, while the potential role of altitude as a modifier for the pseudohypoxia-driven PPGL development is an intriguing connection, the selective reporting of incidence data of PPGL and failure to recognize the increase in incidence over time severely limits the value of the performed meta-regression analysis. While our re-analysis does not rebuff the altitude theory, we hope it may provide data for a more critical discussion of the theory.

Figure 1

Meta-regression for (A) altitude and (B) calendar year using annual incidence rates. S.E. was calculated for all papers with Poisson based on the number of patients and the population at risk in each year. This was done to present data in a unified way, since CIs were not available in all papers.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this letter.

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