

Request for clarification from Ruiter et al regarding ‘Risk of cancer in patients on insulin glargine and other insulin analogues in comparison with those on human insulin: results from a large population-based follow-up study’. Reply to Carstensen B [letter]

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To the Editor: We highly appreciate Dr Carstensen’s interest [1] in our study [2]. With regard to the first question, HRs are not reported per year but refer to the total period of exposure. We referred to an earlier paper from one of us in which an example on thiazide diuretics and hip fracture is described to explain how we usually analyse drug exposure as a time-dependent variable with categories for different durations of use [3]. On reading the first question by Dr

Carstensen [1], we realise that the reference may have been confusing because in the current study we made a direct comparison between insulin glargine (A21Gly,B31Arg, B32Arg human insulin), other insulin analogues and human insulin in which, at the moment a tumour was diagnosed, the insulin exposure status (insulin glargine, human analogues or human insulin) in those diagnosed with cancer was compared with the exposure status of the remainder of the cohort members at the same day of follow-up since starting on insulin. In this way, our HR of 0.7 was an overall HR.

The second question concerns the assumption of equality of risks of cancer at initiation. As all cohort members were followed as of their first use of insulin after earlier use of oral glucose-lowering drugs, the assumption that their cancer risk at start of follow-up is more or less similar does not seem unrealistic. Although one can never exclude the chance of ‘confounding by indication’ with these drugs in the treatment of diabetes mellitus, with regard to the risk of cancer, few doctors will prefer one type of insulin over the other in people without known cancer (the situation in our study population at baseline) as all insulin types are suspected as potentially carcinogenic because of their growth-promoting properties. Moreover, we adjusted for baseline differences where possible. However, to address the concerns of Dr Carstensen, we performed another sensitivity analysis. We included an additional variable in the model indicating whether a participant used insulin glargine at baseline (yes/no) and another variable indicating whether a participant used other insulin analogues at baseline (yes/no).

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These additional analyses did not change the point estimates: for insulin glargine an HR of 0.75 was found (95% CI 0.71, 0.79) and for other insulin analogues an HR of 0.85 was found (95% CI 0.81, 0.88) in comparison with human insulin. This does not surprise us, as adjustment for propensity scores also did not change our results. However, we concluded that a risk difference at baseline cannot be excluded, partly because an intention-to-treat ('fixed') analysis also showed a lower risk of cancer in users of insulin glargine.

Contribution statement All three authors actively participated in the conception and design, or analysis and interpretation of data; drafted the response or revised it critically for important intellectual content; and approved the version for publication.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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