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# Reply to 'Comment on 'New-onset type 2 diabetes, elevated HbA1c, anti-diabetic medications, and risk of pancreatic cancer''

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**Sir,**

We appreciate the interest of Badrick *et al* in our study, expressed in the paper 'Comment on 'New-onset type 2 diabetes, elevated HbA1c, anti-diabetic medications, and risk of pancreatic cancer''. Just like the authors pointed out, there were some limitations in this study, for example, incomplete data on HbA1c and the complex timing relationship between pancreatic cancer and diabetes. We have realised the limitations and addressed them in our study on page no's 1607, 1612 (with citations of Pannala *et al*, 2008; Pannala *et al*, 2009; Giovannucci *et al*, 2010; Aggarwal *et al*, 2012; Sah *et al*, 2013; Chari, 2014) and 1613. However, we understand that it is a difficult question, which may need some further clarifications. Consequently, we have done an additional analysis with 2 years lag time and answered the comments of Badrick *et al* as follows.

If we have understood correctly, the first point regarding 'the diagnosis of diabetes and the diagnosis of a new cancer commonly occur' is basically the same as the last point 'the unique existence of pancreatic-cancer associated diabetes (Pannala *et al*, 2009), where new-onset diabetes might be a clue to early diagnosis of 'silent' pancreatic cancer'. In our paper, we have performed 1 year lag-time analysis (Supplementary Table 1, Lu *et al*, 2015). The results are quite similar to the main analysis. For example, the risk of pancreatic cancer in diabetes in the 1 year lag-time analysis (OR 2.04, 95% CI, 1.56, 2.66) is slightly lower than the overall result (OR 2.16, 95% CI, 1.72, 2.72). To answer the author's hypothetical conclusion 'after excluding cancers detected in the first two years after diabetes diagnosis, there was no association between diabetes and latter pancreatic cancer incidence', we have added the results for 2 years lag time that is attached to this response (Supplementary Table 3). The OR of diabetes relative to the risk of pancreatic cancer is 1.76 (95% CI, 1.32, 2.34). Certainly, there seems to be a trend towards reducing risk estimates as we use longer lag-time analyses, which confirms that detection bias around the time of new-onset diabetes exists to some extent. However, we can safely state that the 2 year lag-time analysis remains consistent with our hypothesis and conclusion, showing that diabetes is still a risk factor of pancreatic cancer 2 years after its diagnosis.

For the second question regarding the relationship between HbA1c and cancer, we have showed the results in Table 2 in our original paper (Lu *et al*, 2015). Despite of only few individuals with data on HbA1c (70% missing), we were able to show the results between the relative measure of HbA1c at diagnosis of diabetes (normal = reference, high = OR 0.57, 95% CI, 0.19, 1.70; very high = OR 1.02, 95% CI, 0.51, 2.03) and 'HbA1c at index date' (normal = reference, high = OR 0.51, 95% CI, 0.17, 1.54; very high = OR 1.85, 95% CI, 0.91, 3.73), a U-shaped relationship between the level of HbA1c and the risk of pancreatic cancer was there. As soon as we used the difference of HbA1c between diagnosis of diabetes and index date, the results showed significantly increased risk of pancreatic cancer. We admit that the results might not be as robust due to incomplete data. This is a common drawback in the Real World data and we have addressed it as a big limitation in our paper (page no. 1613) and call on further studies with robust data.

All the authors have contributed to the answers and we all agree with this response letter.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## REFERENCES

Aggarwal G, Ramachandran V, Javeed N, Arumugam T, Dutta S, Klee GG, Klee EW, Smyrk TC, Bamlet W, Han JJ, Rumie Vittar NB, de Andrade M, Mukhopadhyay D, Petersen GM, Fernandez-Zapico ME, Logsdon CD, Chari ST (2012) Adrenomedullin is up-regulated in patients with pancreatic cancer and causes insulin resistance in beta cells and mice. *Gastroenterology* **143**(6): 1510–1517.

Chari ST (2014) New-onset diabetes: a clue to the early diagnosis of pancreatic cancer. *JOP* **15**(5): 529.

Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D (2010) Diabetes and cancer: a consensus report. *Diabetes Care* **33**(7): 1674–1685.

Lu Y, Rodríguez LAG, Malgerud L, González-Pérez A, Martín-Pérez M, Lagergren J, Bexelius TS (2015) New-onset type 2 diabetes, elevated HbA1c, anti-diabetic medications, and risk of pancreatic cancer. *Br J Cancer* **33**(113): 1607–1614.

Pannala R, Leirness JB, Bamlet WR, Basu A, Petersen GM, Chari ST (2008) Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. *Gastroenterology* **134**(4): 981–987.

Pannala R, Basu A, Petersen GM, Chari ST (2009) New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. *Lancet Oncol* **10**(1): 88–95.

Sah RP, Nagpal SJ, Mukhopadhyay D, Chari ST (2013) New insights into pancreatic cancer-induced paraneoplastic diabetes. *Nat Rev Gastroenterol Hepatol* **10**(7): 423–433.

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