

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14782-review.doc).

Title: Association of type 2 diabetes mellitus and the risk of colorectal cancer; a meta analysis and systematic review

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The manuscript has been improved according to the suggestions of reviewers: Format has been updated

REVIEWER 1

1. Data retrieval is from Medline, EMBASE, Cochrane Library, and ISI Web of knowledge databases, but in Figure 1 it is only from PubMed ?

Answer;

The databases mentioned in the figures are adjusted now

2. 2、 Is it accurate that ‘CRC is the second leading cause of cancer-related deaths world-wide and New onset of DM is invariably considered as a marker of occult cancer, or of progression of a known disease ‘?

Answer

3. Yes. Its accurate and this finding is endorsed by a reference as well
4. Is there an offset error that obesity may be affect the onset risk both DM and CRC?

Answer; Yes, it can be. But not related to the present study

REVIEWER 2

1. This is a meta analysis & systematic review for association of CRC with DM. Please explain why you have excluded the 32 case-control studies.

Answer; 32 case-control studies were excluded as these studies explored the risk of all cancers in diabetic patients. The current meta analysis focused on the risk of CRC in diabetic patients.

2. How to prove your statement 'DM was associated with an increased risk (RR; 1.40; 95% CI: 1.20–1.63) for death from CRC.' The argument is the increased mortality among diabetic patients is actually due to diabetic complications rather than CRC per se. Please provide clear view.

Answer; Agreed with this valuable observation. I've adjusted the text accordingly.

3. The statement 'New onset of DM is invariably considered as a marker of occult cancer, or of progression of a known disease (reverse causality: diabetes is a consequence of cancer) (28)' This is very strong statement, new onset DM is not always indicate occult cancer or progression of cancer. It may indicate pancreatic cancer however. But this is not the case in every patient.

Answer; Reference 28 is a large cohort study which showed 15% excess mortality risk for cancers in diabetics. This could be partly due to reverse causality, or to decreased survival of cancer patients with diabetes. This is a very new research and I have mentioned in my article for sharing this finding with the scholarly community.

4. The statement of 'CRC risk increased in diabetic men, but not women, before DM onset' is not clear and doesn't make sense .Please explain or re-phrase.

Answer; I have rephrased the sentence for better understanding.

5. Other important studies are not included ,as example: 1.P.T. Campbell, E.T. Jacobs, C.M. Ulrich, J.C. Figueiredo, J.N. Poynter, J.R. McLaughlin, R.W. Haile, E.J. Jacobs, P.A. Newcomb, J.D. Potter, L. Le Marchand, R.C. Green, P. Parfrey, H.B. Younghusband, M. Cotterchio, S. Gallinger, M.A. Jenkins, J.L. Hopper, J.A. Baron, S.N. Thibodeau, N.M. Lindor, P.J. Limburg, M.E. Martinez, for the Colon Cancer Family Registry. (2010) Case-control study of obesity, overweight and colorectal cancer risk, overall and by tumor microsatellite instability status. Journal of the National Cancer Institute, 102 (6): 391-400. PMID: 20208017. 2.P.T. Campbell, C.C. Newton, A.N. Dehal, E.J. Jacobs, A.V. Patel, S.M. Gapstur. (2012) Impact of body mass index on survival after colorectal cancer diagnosis: the Cancer Prevention Study-II Nutrition Cohort. Journal of Clinical Oncology, 30 (1): 42-52. PMID: 22124093 A.N. Dehal, C.C. Newton, E.J. Jacobs, A.V. Patel, S.M. Gapstur, 3.P.T. Campbell. (2012) Impact of diabetes mellitus and insulin-use on survival after colorectal cancer diagnosis: the Cancer Prevention Study-II Nutrition Cohort. Journal

of Clinical Oncology, 30 (1): 53-59. PMID: 22124092 Other studies that are related as well before 2010:1 Will JC, Galuska DA, Vinicor F, Calle EE. Colorectal cancer: another complication of diabetes mellitus? Am J Epidemiol 1998;147:816-25. 2 Hu FB, Manson JE, Liu S, Hunter D, Colditz GA, Michels KB, et al. Prospective study of adult onset diabetes mellitus (type 2) and risk of colorectal cancer in women. J Natl Cancer Inst 1999;91:542-7. 3 Limburg PJ, Anderson KE, Johnson TW, Jacobs DR Jr, Lazovich D, Hong CP, et al. Diabetes mellitus and subsite-specific colorectal cancer risks in the Iowa women's health study. Cancer Epidemiol Biomarkers Prev 2005; 14:133-7. 4 Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Preliminary communication: glycated hemoglobin, diabetes, and incident colorectal cancer in men and women: a prospective analysis from the European prospective investigation into cancer-Norfolk study. Cancer Epidemiol Biomarkers Prev 2004;13:915-9. 5 Dawson SI. Long-term risk of malignant neoplasm associated with gestational glucose intolerance. Cancer 2004;100:149-55. 6 Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol 2004;159:1160-7. 7 Meyerhardt JA, Catalano PJ, Haller DG, Mayer RJ, Macdonald JS, Benson AB 3rd, et al. Impact of diabetes mellitus on outcomes in patients with colon cancer. J Clin Oncol 2003;21:433-40. 8 Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet 2004;363: 1346-53. 9 Wu Y, Yakar S, Zhao L, Hennighausen L, LeRoith D. Circulating insulin-like growth factor-I levels regulate colon cancer growth and metastasis. Cancer Res 2002;62:1030-5. 10 Ma J, Giovannucci

Answer; Thanks for the references. In fact there is a limit in quoting the references and including them in the meta analysis and systematic reviews. I have selected the most relevant references for the current meta analysis

REVIEWER 3

in my opinion very good piece of work - methodology well done systematic review performed well;

Answer

hows I appreciate valuable observations

