Pursuant to the request from Professor Eero Pukkala (Finnish Cancer Registry), I have read and reviewed the article by Anna But et al., “Assessing the effect of treatment duration on the association between anti-diabetic medication and cancer risk”, PLoS ONE, Nov 2016.

Numerous epidemiologic studies have found associations between diabetes and cancer. While the findings indicate an increased and consistent risk of cancer for type 2 diabetes, the strength of relationship depends on the specific site of the malignancy. The strongest relations have been shown for liver and pancreatic cancers, whereas prostate cancer is less likely to occur in men with type 2 diabetes. For other cancers, the populations sizes are often small, but for lung and ovarian cancer and the associations appear to be inconsistent.

An evaluation of the effect of treatment duration was done for all cancer sites combined by contrasting the risks for non-users (n = 1,028 cases) and users (n = 53) of ADM. As admitted by the authors, the amount of information in the data was few, characterized by the small number of exposed cases was small, which did not permit a sufficiently detailed stratification. Thus it was not possible to carry out the modeling and estimation of exposure effects, as well as to accommodate effect modification and confounding by risk factors, separately for the 18 specific cancer sites (Table S2). The authors did not state at the outset of the study which ADMs they thought might be related to cancer risk, based on prior knowledge. The estimation of the overall risk of cancer could conceal the underlying manifestations caused by the operation of the site-specific cancer risks.

Many studies have suggested that metformin could potentially reduce cancer risk. Recently, Golozar et al. (2016) pointed out that the validity of this purported reduction in cancer risk have been limited by methodological flaws either in the study design or in the data analysis.

**Article Does Metformin Reduce Cancer Risks? Methodologic Considerations**

The conclusion in the Abstract of the present study was: "No significant difference in cancer risk between users [of ADT] and non-users was observed after adjustment." However, a prominent exception was oral metformin treatment for a duration of 1-4 years (Table 3). The risk ratio estimates from Model I (adjusted for age, gender, calendar time) and Model II (adjusted in addition for BMI, smoking status, interaction of age and gender, age and BMI) were approximately at the same elevated level: 1.47 (1.0-2.1) and 1.41 (0.9-2.0), respectively. Although the lower limit of the 95% confidence interval for the latter estimate of RR failed to exceed 1.0 (consistent with P = 0.05), because of the small number of exposed cases, the authors stated in the Discussion cautiously: "We found that those who had used ADM, particularly metformin, for 1-4 years ... might be at higher risk of cancer." It is well known that metformin, because of its exceptional effect mechanism, does not cause hypoglycemia and is the primary oral ADM for type 2 diabetes for overweight persons, but especially when taken together with large quantities of alcohol it can be lethal. Models I & II were not adjusted for the intake amount of alcohol. Caution is also needed for an interaction effect when metformin is administered together with insulin (use of oral ADM ≤ 3 years and insulin, RR ≈ 2.27, P ≈ 0.06, Table 3).
An interesting finding is that the risk of cancer was lower in those with moderate use of alcohol when compared to non-drinkers, whereas no significant difference was seen between heavy drinkers and abstainers (Table S3). This may well be so, but one should first check whether the scaling of the determinant (alcohol use) of the outcome event (cancer incidence) was chosen specifically for the study at hand. A good epidemiologic research practice is to use a scaling that is in line with the generally accepted one. This is because it allows the comparison of the results from the present study to those derived from previous studies.

The scale for alcohol use was coded as: moderate users, < 14 portions (12 g of pure alcohol) per week for men, < 7 portions for women; heavy users, ≥ 14 portions per week for men, ≥ 7 portions per week for women. The recommended risk levels for alcohol drinking in Finland are the following: moderate drinkers, 14 portions (12 g of pure alcohol) per week for men, 7 portions for women; heavy drinkers, 24 portions per week for men, 16 portions per week for women (The Finnish Medical Society Duodecim, 15.10.2015). [http://www.kaypahoito.fi/web/kh/suositukset/suositus?id=hoi50028](http://www.kaypahoito.fi/web/kh/suositukset/suositus?id=hoi50028)

These risk levels set the limit for the use of alcohol whose exceedance probably entails harmful health manifestations. Therefore, men enrolled in the present study were classified as heavy users if they reported to have consumed at least 14 portions of alcohol in a week. But they could have drunk 14-23 portions of alcohol in a week, and they would not be regarded as heavy users according to the Duodecim risk scale. Moreover, people tend to underreport their abuse of alcohol when inquired. The empirical scaling of alcohol use influences the relative sizes of the compared sub-populations, and therefore may have bearing on the drawn statistical inference.

The methodological advantage in the But et al.’s study was that they evaluated changes in cancer incidence in relation to the duration of diabetes treatment in data sets formed by a Lexis diagram. When the research interest is in transition between health/disease outcome states (e.g. cancer-free, ill with cancer, cancer in remission, death from cancer) an alternative approach, stochastic process analysis, is applicable via multistate modeling using a logistic regression from aggregate sequential cross-sectional survey data.

The authors have to be commended for undertaking and completing such a demanding study which was made possible by the availability of Finnish population systems and medical register bases. Their application of the Tabulation outline and the EPI: R package presents a fine epidemiologic research study example.

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