Reviewer’s report

Title: Association between Variations in the Fat Mass and Obesity-Associated Gene and Pancreatic Cancer Risk: A Case-Control Study in Japan

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Reviewer: Jianjun Zhang

Reviewer’s report:

Pancreatic cancer is a leading cause of cancer death in Western countries, and its incidence rates are increasing in some Asian countries. Given the rapid fatality of and lack of screening tools for this malignancy, it is important to identify its environmental and genetic risk factors. This paper investigated a SNP (rs9939609) in the fat mass and obesity-associated gene (FTO) and its interaction with BMI and diabetes in relation to pancreatic cancer risk. The research questions addressed in this study were significant and timely, and it offers some novel data for the etiology and pathogenesis of pancreatic cancer. However, several issues in the design, analysis, and interpretation of the study need to be carefully considered.

Minor Essential Revisions:

1. rs9939609 is a variant located in the first intron of the FTO gene. The functionality of this polymorphism largely remains unclear. The rationale for selecting this variant should be addressed in more detail.

2. As mentioned by the authors, at least 30 loci (including rs9939609) have been linked to BMI and obesity in genome-wide association studies. Did the authors evaluate the effects of some or all remaining SNPs on pancreatic cancer risk? If yes, what were the results? Were there any significant interactions between rs9939609 and other SNPs? If not, why not?

3. A response rate of 85% among cases was reported in this study. This is quite high for pancreatic cancer. Were the cases who died before the interview considered in the calculation of the response rate? It was also stated that a rapid case ascertainment system was used to recruit patients diagnosed with pancreatic cancer. What were the median and/or mean numbers of days between the diagnosis of pancreatic cancer and the interview of cases?

4. Controls were recruited from inpatients and outpatients. What were the diseases for which those patients sought medical care in the study hospitals? Were those diseases associated with BMI or obesity (risk factors examined in this study)?

Discretionary Revisions:

1. A potential interaction between rs9939609 and diabetes was detected in
relation to pancreatic cancer risk. It should be more cautious to mention “the presence of a multiplicative interaction …” (page 10) as p for interaction was 0.28.

2. It is better to combine the TA genotype with AA genotype in the evaluation of gene effect as only three cases and one control were homozygous for the A allele among subjects with BMI #25 (Table 3).

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.