Author's response to reviews

Title: A case-control study on the effect of Apolipoprotein E genotype on gastric cancer risk and progression

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Author's response to reviews: see over
Dear Editor,

I am very glad to read the reviewers’ reports and suggestion to improve the quality of the manuscript, and I hope the major and minor revisions implemented in this revised version are satisfactory for its publication.

In this version the comments of the reviewers have been addressed separately and a point-by-point response to the concerns is provided below. Changes in the text are marked with the blue colour.

With many thanks for your assistance.

Best regards,
Stefania Boccia
1st reviewer: A. Bennet

Reviewer's report:
A well-formulated, medically and epidemiological sound hypothesis lays the ground to this manuscript. There are some concerns regarding the method.

We thank the reviewer for the favourable report on our manuscript.

Major Compulsory Revisions

The control group consists of “cancer-free patients, with a broad range of diagnoses, admitted to the same hospital during the identical time period”. As ApoE4 is commonly over-represented amongst patients with cardiovascular diseases, and as this patient group is common at hospitals, I fear that the current control group may lead to false risk estimations. Please show that your control group is representative of the population. Otherwise, a population-based control group should be used.

That’s true! The control group should be better characterized. Closer details about our control population have been added in the revised version of the MS (page 6, lines 8-12). Briefly, about 50% of our control population is made of blood donors while the other half is made of patients undergoing surgical interventions for acute diseases as laparoscopic cholecystectomy or appendicitis or inguinal hernia and a smaller portion of patients affected by chronic disease as hypertension or Chronic Obstructive Pulmonary Disease (COPD) undergoing periodical check-up. Accordingly, cardiovascular disease cannot be considered a common condition in our control population.

I appreciate that gastric cancer is a relative uncommon disease, but with 156 cases there are only 15 e2/e3 carriers and no e2/e2 carriers in the patients group. The power of the study clearly confirms this. The study would benefit from more cases being included.

That’s true! As you can see, the need to increase the study’s sample size has been acknowledged in the discussion section as a limitation of the study (page 10, 5th and 6th lines from the bottom).

Third: It is inappropriate to calculate the risk for the combined e2/e2 and e2/e3 and e3/e4 and e4/e4 when there are no cases with the homozygous genotypes in the case-control material.

As concerning statistics performed in the MS, separate analyses were conducted for each of six ApoE genotypes and for ε2 and ε4 carrier status by excluding the genotype ε2ε4. Even if it’s quite uncommon to combine different genotypes when there are no cases with the homozygous genotype, previous similar examples can be found in literature (eg: Demirag MD et al, 2007).
2nd reviewer: Jan O Aasly

Reviewer's report:
The authors genotyped fifty-six gastric cancer cases and 444 hospital controls for apoE polymorphism (ε2, ε3, ε4 alleles). The relationship between GC and putative risk factors was measured using the adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) from logistic regression analysis. Subjects carriers at least one apoE ε2 allele had a significant 60% decrease of GC risk compared with ε3 homozygotes. No significant interaction emerged between the ε4 or ε2 allele and environmental exposures, nor ε2 or ε4 alleles affected the median survival times, even after correcting for age, gender and stadium. They concluded that the ε2 allele may have a protective effect against GC. The study sample size comprised 156 cases and 444 controls, with a participation rate of 98% among cases and 93% among controls.

In table 2, 152 GC cases and 402 controls are genotyped which is a much lower percentage than 98% and 93%, why? Was this due to genotyping problems? The number of genotyped cases and those responding to environmental studies should be the same. The observed discrepancy is due to problems occurred during the genotyping process. As previously shown (Trompet S et al., 2009), it’s not a rule that genotyped subjects have to be the same enrolled into the study. To clarify such difference a footnote has been added to the 2nd table.

How was the controls selected? The control group is in many ways quite similar to the GC group. The data on serum cholesterol levels were not available. However, was there any data on use of statins? There are results suggesting that statins may reduce the risk of gastric cancer and data for statin use could be a surrogate marker for abnormal lipid metabolism. That's a good point but unfortunately data on use of statins are not available in our study population.

In table II the authors should change "NC: not calculable due to few many values" Many thanks, mistake corrected as suggested.