This paper examines the gene-gene interaction between two common polymorphisms (MnSOD Val16Ala and GPX-1 Pro198Leu) and breast cancer risk in a nested case-control study from the Nurses Health Study cohort. The authors found that, although neither allele alone was associated with a change in breast cancer risk, an increase in risk was observed in individuals who were homozygous for both the MnSOD Ala16 allele and the GPX-1 Leu198 allele. This paper contributes to the literature by simultaneously examining two genes involved in the antioxidation process potentially associated with breast cancer risk.

In the Introduction, the authors hypothesized that being homozygous for the less active form of both genes increases breast cancer risk. But in their analysis of MnSOD, they look at individuals homozygous for the Ala allele. According to Sutton (whom Tamimi et al. 2004 in the previous paper of this nested case-control study quotes), the Ala allele is the more active form of the gene, showing superior efficiency over the Val allele of MnSOD import into the mitochondrial matrix. While arguments can be found in the literature for both the benefits and the drawbacks of increased activity, the functional evidence shows that the Ala allele is more active than the Val allele. Therefore, the authors need to justify their consideration of the MnSOD Ala16 allele as the less active form or, otherwise, the biological plausibility of an interaction between the MnSOD Ala16 and the GPX-1 Leu198 alleles.

1) For consistency, MnSOD and GPX-1 should be italicized in the results section of the abstract.
2) In the first sentence of the Introduction, â€œsuper oxideâ€ should be one word.
3) In the third paragraph of the Introduction, the old dbSNP identifier for Val16Ala (rs1799725) should be replaced with the new dbSNP identifier (rs4880).
4) The list of covariates in the multivariate models presented on page 4 is different from that in the footnotes of table 1.
Declaration of competing interests:

I declare that I have no competing interests.