

RESPONSE

Concerning the *CYP17 MSPA1* polymorphism and breast cancer risk: a meta-analysis

Zheng Ye¹ and James M. Parry²

^{1,2}Centre for Molecular Genetics and Toxicology, School of Biological Sciences, University of Wales, Swansea, Singleton Park, Swansea, SA2 8PP, UK

Feigelson and colleagues have raised some important points concerning the selection of the data sets and the application of meta-analysis to resolve some of the problems associated with determining the relationships between metabolic polymorphisms and susceptibility to various disease conditions. In recent years, many meta-analyses have been published with the aim of providing more objective and quantitative summaries of genetic association studies (Lau *et al.*, 1998; Dunning *et al.*, 1999; de Jong *et al.*, 2001). However, there are always concerns that combining studies with different degrees of bias and studies of different quality may produce different conclusions (Lau *et al.*, 1998).

Feigelson *et al.* argue in their letter that meta-analysis is not the best approach to resolve possible *CYP17*–breast cancer associations because of the different experimental designs and the mixtures of age and ethnicities in the data sets. In our paper table I (Ye and Parry, 2002) illustrates that many of the individual studies are of limited size and thus lack the power to clarify a possible *CYP17*–breast cancer association. Thus, we attempted to reduce this lack of power by combining data sets in a meta-analysis. In our paper we attempted to carefully evaluate the nature of the available data, including factors such as duplications, familial disease and male breast cancer studies. Before the studies were pooled for analysis, tests for heterogeneity across the studies were performed and they indicated no evidence of heterogeneity between the individual studies that were related to *CYP17 MspA1* polymorphism. This indicated that the data from the selected studies were suitable for pooled analysis using the Mantel–Haenszel method (Mantel and Haenszel, 1959). The results of our meta-analyses have been strongly supported by a recent study of de Jong *et al.* (2002). Their meta-analysis of 10 *CYP17 MspA1* studies indicated that overall odds ratios (ORs) of breast cancer associated with the combined variant and the homozygous genotype were 0.99 (95% CI 0.88–1.11) and 1.05 (95% CI 0.89–1.23), respectively, which were similar to the results of our pooled analyses across 15 studies. In our paper the overall ORs of breast cancer susceptibility associated with the combined variant and the homozygous genotype were 0.98 (95% CI 0.89–1.07) and 1.05 (95% CI 0.87–1.21), respectively.

Although Feigelson *et al.* appreciate that differences in ages and ethnic groups may impact on the evaluation of the *CYP17*–breast cancer association, they combined different ethnic

groups in their analysis of a possible *CYP17*–breast cancer association in their two recent studies; The study of Feigelson *et al.* (1997) combined three ethnic groups (Asians, African-Americans and Latinos) and found an increased risk of breast cancer in women carrying at least one A2 allele, with an especially large increased risk of developing advanced breast cancer. The same situation is found in another study (Feigelson *et al.*, 2001), in which data from different ethnic groups in the cases (African-Americans, Latinos, Caucasians and Japanese) were combined when analyzing the breast cancer risk, where they found a small increased risk of advanced breast cancer. In table II of our paper (Ye and Parry, 2002), we can see that most of the studies based upon a single ethnic group did not find such an association. We therefore concluded that the results of Feigelson *et al.* (1997, 2001) highlight the problems of combining different ethnic groups, a topic which we discussed in our paper.

It is not surprising that the summary estimate of Feigelson *et al.* for the influence of the A2/A2 allele on advanced breast cancer is different from ours since they included their recent data (Feigelson *et al.*, 2001) and that of three other studies. We fully admit that the ORs in some studies computed by comparing advanced to localized cases are not as precise as those obtained by comparing advanced to unaffected controls. However, when comparing table II in our paper with table I of Feigelson *et al.* we can see that the ORs computed by these two methods are not clearly different. Other differences in data usage can be seen in Table I of Feigelson *et al.*, where they used the case–control data for post-menopausal breast cancer (112/277) from the study of Mitrunen *et al.* (2000) but did not include the case–control data for pre-menopausal breast cancer (67/203).

The nested case–control study of Feigelson *et al.* (2001) contains 235 cases of advanced breast cancer, which represents the largest number of advanced cases for any individual study thus far. The three other studies they included (Helzlsouer *et al.*, 1998; Kristensen *et al.*, 1999; Mitrunen *et al.*, 2000) contain only 351 advanced cases. When a pooled analysis was performed based on these four studies, the results are strongly influenced by the data from the largest study (Feigelson *et al.*, 2001), which greatly impacts on the final summary estimate. However, as we mentioned above, we have strong reservations concerning the combination of data from different ethnic groups, as performed by Feigelson *et al.* (2001). The different conclusions reached by us and Feigelson and colleagues concerning the association between the *CYP17 MspA1* polymorphism and breast cancer risk clearly illustrates to the readers of *Mutagenesis* the unresolved problems of the selection of appropriate data sets in reaching definitive answers on cancer susceptibility.

¹To whom correspondence should be addressed. Email: bazhey@swansea.ac.uk

References

- de Jong,M.M., Nolte,I.M., te Meerman,G.J., van der Graaf,W.T.A., Oosterwijk,J.C., Kleibeuker,J.H., Schaapveld,M. and de Vries,E.G.E. (2002) Genes other than *BRCA1* and *BRCA2* involved in breast cancer susceptibility. *J. Med. Genet.*, **39**, 225–242.
- Dunning,A.M., Healey,C.S., Pharoah,P.D.P., Teare,M.D., Ponder,B.A.J. and Easton,D.F. (1999) A systematic review of genetic polymorphisms and breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.*, **8**, 843–854.
- Feigelson,H.S., Coetzee,G.A., Kolonel,L.N., Ross,R.K. and Henderson,B.E. (1997) A polymorphism in the *CYP17* gene increases the risk of breast cancer. *Cancer Res.*, **57**, 1063–1065.
- Feigelson,H.S., Mckean-Cowdin,R., Coetzee,G.A., Stram,D.O., Kolonel,L.N. and Henderson,B.E. (2001) Building a multigenic model of breast cancer susceptibility: *CYP17* and *HSD17B1* are two important candidates. *Cancer Res.*, **61**, 785–789.
- Helzlsouer,K.J., Huang,H.Y., Strickland,P.T., Hoffman,S., Alberg,A.J., Comstock,G.W. and Bell,D.A. (1998) Association between *CYP17* polymorphisms and the development of breast cancer. *Cancer Epidemiol. Biomarkers Prev.*, **7**, 945–949.
- Kristensen,V.N., Haraldsen,E.K., Anderson,K.B., Lønning,P.E., Erikstein,B., Kareson,R., Gabrielsen,O.S. and Børresen-Dale,A.L. (1999) *CYP17* and breast cancer risk: the polymorphism in the 5' flanking area of the gene does not influence binding to Sp-1. *Cancer Res.*, **59**, 2825–2828.
- Lau,J., Ioannidis,J.P.A. and Schmid,C.H. (1998) Summing up evidence: one answer is not always enough. *Lancet*, **351**, 123–127.
- Mantel,N. and Haenszel,W. (1959) Statistical aspects of the analysis of data from retrospective studies of disease. *J. Natl Cancer Inst.*, **22**, 719–748.
- Mitrunen,K., Jourenkova,N., Kataja,V., Eskelinen,M., Kosma,V.M., Bebenhamou,S., Vainio,H., Uusitupa,M. and Hirvonen,A. (2000) Steroid metabolism gene *CYP17* polymorphism and the development of breast cancer. *Cancer Epidemiol. Biomarkers Prev.*, **9**, 1343–1348.
- Ye,Z. and Parry,J.M. (2002) The *CYP17* *MspA1* polymorphism and breast cancer risk: a meta-analysis. *Mutagenesis*, **17**, 119–126.