LETTERS TO THE EDITOR


Alfredo Morabia, Martine Bernstein and Stephane Heritier
Hôpital Cantonal, Rue Micheli-du-Crest 24, CH 1211 Genève 14, Switzerland

Dear Sir,
Hunter et al. have computed the relative risks (RRs) of smoking and breast cancer among women with the slow acetylator genotype using as reference group non-smoking rapid acetylators.

This way of analysing their data tends to pull the relative risk towards unity and therefore to attenuate the apparent effect of smoking among slow acetylators. In Table III, for example, the multivariate RR of breast cancer among current smokers of 15+ cigarettes daily who are slow acetylators is 1.5 (0.7–3.2) relative to never-smoking rapid acetylators. This same relative risk would be 1.9 if it were computed relative to never-smoking slow acetylators (1.5/0.8 = 1.9). For the same reason, the RRs shown in Tables III–V for slow acetylators should all be incremented by a factor 1.25 (1/0.8). The rationale for using never-smoking rapid acetylators instead of never-smoking slow acetylators needs to be explained by the authors since it is inconsistent with the tests for interaction reported in their paper. These tests compare the effect of smoking in slow acetylators versus the effect of smoking in rapid acetylators. Unfortunately, readers cannot recompute the RRs and their confidence limits on the basis of the data given in the tables since this is a matched study.

We would be therefore very grateful to Hunter et al. if they could present all the matched and multivariate RRs among slow acetylators using never-smoking slow acetylators as reference.

Response

David Hunter, Dorota Gertig and Donna Spiegelman

Dear Sir,

We thank Dr Morabia and colleagues for their comments. There are several models of interaction that can be applied to the cross-classification of categories of environmental exposures with strata of genotype (1). We chose a model that does not assume that there is no effect of genotype in the lowest category of exposure, by comparing all combinations of genotype and smoking category with the hypothesized low-risk group (NAT2 rapid acetylators/never smokers). This model is conservative in that it does not force the odds ratio (OR) for slow acetylators/non-smokers to equal 1.0.

In any case, using the alternative model does not materially alter the results of our study. Space does not permit repetition of all tables in our paper, but as illustration we present the results for Tables III and IV. In each case, the ORs and 95% confidence intervals (CIs) in the stratum of rapid acetylators are unchanged. Setting the OR for slow acetylators/never smokers to 1.0, the ORs and 95% CIs are 1.3 (0.9–2.0) for past smokers, 1.4 (0.5–3.6) for current smokers of 1–14 cigarettes/day and 1.9 (0.9–3.8) for smokers of 15+ cigarettes/day (Table III, smoking status defined immediately prior to diagnosis). Similarly, for smoking defined 10 years prior to diagnosis (Table IV), the ORs and 95% CIs in the slow acetylator stratum are 1.3 (0.8–1.9) for past smokers, 2.5 (1.1–5.7) for current smokers of 1–14 cigarettes/day and 1.6 (0.9–2.8) for current smokers of 15+ cigarettes/day. Although the point estimate for the smokers of 1–14 cigarettes/day is statistically significant, the P-value for interaction is not, and in view of the multiple comparisons being made and the non-linearity of the dose–response, we would be reluctant to attach importance to this one significant point estimate. The test for interaction we used in Tables III and IV tests the difference in log likelihood of the model with terms for genotype, indicator variables for smoking and other covariates versus the model presented in the tables with the cross-classified gene by smoking variables plus covariates. This test is equivalent to comparing the log likelihoods of the first model with the first model plus cross-product terms of gene by smoking variable interactions, plus covariates. We feel that this test is an appropriate test of the interaction being tested, in particular as the smoking variable cannot be configured as an ordered categorical variable as it would not be appropriate to model never, past and current smoking as an ordered variable. In Table V (using smoking pack-years), because pack-years is an ordered categorical variable, the Wald test is an option for testing for interaction with acetylation genotype. In Table V, the Wald test for interaction was non-significant, P = 0.15.

The fact that several different choices of referent category can be proposed for data where genotype and an exposure variable are cross-classified poses a difficult problem in the study of gene–environment interactions. To perform several tests based on several models of interaction would be a form of multiple comparisons testing, and increases the possibility of a false positive result. In our study, we presented the interaction in a manner we had proposed a priori to the analysis. Further discussion of which model or models of interaction should be the default in studies of gene–environment interaction is warranted.

Reference