Studies using tumor markers should consider the likelihood of misclassification among the different outcome categories. Sensitivity analyses applying different assumptions about the rates of misclassification will be helpful in interpreting studies with polytomous outcomes particularly when the overall results, such as those of van der Kooy et al. (1), suggest little to no heterogeneity by marker status.

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THE AUTHORS REPLY

Terry and colleagues (1) argued that "Studies using tumor markers should consider the likelihood of misclassification among the different outcome categories." Although we agree with them in general, we think that their concerns are less relevant to our specific study situation (2).

First of all, we would like to emphasize that our main objective was to examine differences in risk profiles between cases with p53+ and p53− breast tumors. Therefore, when interpreting our results we focussed on the case–case comparisons. In a polytomous (3)—rather than polychotomous—logistic regression model, we compared p53+ with p53− cases relative to the same reference group, and we presented odds ratios for both case groups. The test of heterogeneity resulting from this analysis shows whether or not p53− tumors (relative to controls) are differently associated with a particular risk factor compared with p53+ tumors (relative to the same controls). We discussed that misclassification may have biased our risk estimates (meaning the differences in risk estimates for p53+ and p53− tumors) toward unity. This corresponds with the statement of Terry and colleagues that "misclassification of the p53 status..." reduced the "likelihood of finding heterogeneity in risk patterns by p53 status." However, Terry and coworkers argue further that, in addition to the bias in the difference between the odds ratios, the bias in the absolute value of the separate odds ratios for p53+ and p53− tumors deserves more attention. They state that "misclassification of p53 status may likely bias the comparisons of p53+ cases compared with controls toward unity," which is based on a postulated monotonic trend in risks over outcome categories (i.e., stronger associations for p53+ tumors than for p53− tumors). In our opinion, no plausible biologic evidence exists so far to generate such a priori hypotheses. Our main reasons for reporting the odds ratios for the two case groups separately were 1) to provide insight in the directions and strengths of the associations with p53+ and p53− tumors, and 2) to give odds ratio estimates that can be compared with previously reported risk factor associations for breast cancer overall. In the absence of a priori assumptions about trends in risk over outcome categories, a discussion of the effect of misclassification of p53 status on the tumor-specific odds ratios relative to controls is premature and, more importantly, it does not change the results of our tests on heterogeneity in another way than was already discussed.

Furthermore, we would like to stress that misclassification in our study was greatly reduced by an aspect of our study design that seems to have gone unnoticed by Terry and coworkers. Originally, we defined two groups with p53 protein overexpression ("weak nuclear staining of 1–10 percent of tumor cells") scored as intermediate p53 overexpression (p53±) and "dark nuclear staining of more than 10 percent of tumor cells" scored as clear p53 overexpression (p53+) and, one group of cases without p53 overexpression ("showing less than 1 percent stained nuclei" scored as negative (p53−)). We demonstrated that misclassification was most likely to occur in the p53± and p53− groups. Therefore, we excluded the p53± cases from the analysis and compared risk factors only between the extremes, tumors with clear overexpression (p53+) versus those without overexpression (p53−). Thus, we increased the likelihood of detecting heterogeneity in risk factor patterns between p53+ and p53− breast cancer cases.

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