

LETTER

Contralateral breast cancer risk in *BRCA1/2*-positive families needs to be adjusted for phenocopy rates particularly in second-degree untested relatives

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See related research by Rhiem *et al.*, <http://breast-cancer-research.com/content/14/6/R156>

In the previous issue of *Breast Cancer Research*, Rhiem and colleagues [1] report contralateral breast cancer risks in relatives of *BRCA1/2* mutation carriers as well as those testing negative. The authors quote 25-year risks of 44.1% for *BRCA1* and 33.5% for *BRCA2*. The risks quoted are somewhat lower than might be inferred from previous estimates in *BRCA1/2* carriers, which have been as high as 40% at 10 years [2]. This discrepancy may be explained in part by the decision to exclude index cases in which there may have been testing bias to bilateral disease. However, the authors dismiss a second bias of including many non-carriers in their analysis as 'putative' carriers.

Only 319 (16%) out of 1,909 *BRCA1/2* women included in their analysis were proven mutation carriers, and 1,590 relatives were included as first- or second-degree relatives. Interestingly, the authors chose to report the 5% to 6% rate of those affected with breast cancer testing negative (phenocopies) from a Dutch prospective analysis as a reason to dismiss the phenocopy rate as having a major effect in their analysis [3]. However, in this Dutch study, of those with just breast cancer, and not ovarian cancer, 11 (10%) out of 113 tested negative [3]. Indeed, the rate in their own paper was 40 (11%) out of 368 [1]. Given that there was a discrepancy between the 326 carriers in the

text and 319 in their table, it is likely that the authors have also included 'obligate' carriers rather than those directly testing mutation-positive. As such, the authors' phenocopy rate is likely higher in untested relatives. In our series of directly tested first-degree relatives, 50 (17.6%) out of 284 with breast cancer tested negative and 19 (35%) out of 54 second-degree relatives, and this in line with our previous estimates [4]. The authors do not present the proportion of first-/second-degree relatives in their analysis, so it is difficult to determine how large an effect this could have had. Their assumption that they could include 'clusters' of breast cancer to impute which side of the family a mutation may have come from may add to the phenocopy rate. Often, paternally derived mutations are wrongly inferred, at first, to be maternal because of maternally related breast cancers.

Another potential problem with quoting the rates from the paper to women testing positive for mutations today is that the median years of birth for relatives were 1939 for *BRCA2* and 1943 for *BRCA1* and median ages at diagnosis of first breast cancer were 43.5 and 48.1 years for *BRCA1* and *BRCA2*, respectively. This would imply a median year of diagnosis of 1987, when breast cancer rates and, presumably, contralateral rates would have been lower [5].

Authors' response

Rita K Schmutzler, Kerstin Rhiem and Christoph Engel

We thank Evans and colleagues for their valuable comments regarding phenocopies as a potential source of our study. To determine the extent to which phenocopies

could have biased our contralateral breast cancer risk estimates, we performed additional data analyses. The rate of negatively tested breast cancer patients from mutation-positive families in our registry still amounts to 11% (64 out of 558), which is lower than reported by Evans and colleagues. Among all 6,235 relatives who were analyzed in our study, 4,586 individuals (74%) were second-degree relatives. Since the largest proportion of phenocopies is expected in the group of second-degree relatives, we excluded this group from the analysis and

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re-calculated the risks based on first-degree relatives only. The 10-year cumulative risks were 25.8% (95% confidence interval (CI) 21.5% to 30.1%) for those from *BRCA1* families and 15.7% (95% CI 10.4% to 21.0%) for those from *BRCA2* families. These figures are slightly higher than those based on all relatives. If only relatives with a proven mutation are considered, the 10-year cumulative risks were 28.1% (95% CI 19.5% to 36.7%) for *BRCA1* carriers and 20.2% (95% CI 6.9% to 33.5%) for *BRCA2* carriers. Importantly, all of these risks are considerably lower than those obtained from index cases: 38.0% (95% CI 33.9% to 42.1%) for *BRCA1* carriers and 22.5% (95% CI 17.2% to 27.8%) for *BRCA2* carriers.

We agree that quoting risk estimates obtained from retrospective data to women testing positive today holds a number of potential problems. This underlines the urgent need for large and long-term prospective cohort studies to obtain valid risk estimates.

Abbreviation

CI, confidence interval.

Competing interests

The authors declare that they have no competing interests.

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