

Effects of *BRCA1/2* on Ovarian and Breast Cancer Survival—Response

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We thank Gong and colleagues (1) for their thoughtful comments and interest in our meta-analysis of the effects of *BRCA1*- and *BRCA2*-related mutations on ovarian and breast cancer survival (2).

Regarding the first point, we want to point out one advantage of using hazard ratio (HR) as an overall measure of association is that HR is irrelevant to a specific time point (e.g., 5 or 10 years), because HR estimates the true ratio of two underlying hazards and the ratio is assumed to be constant over time. Varying follow-up durations may potentially influence the width of the confidence interval (CI), which is already factored into the calculation of the combined HR. We had repeated the meta-analysis using the 10-year HR estimate from McLaughlin and colleagues (3) instead of the 5-year HR and obtained almost identical results. Meta-analysis does not require studies to have comparable follow-up. We believe that our combined HR as an overall measure of association remains valid.

Regarding the second point, the *P* value of 0.008 reported in Boyd and colleagues (4) was based on a log-rank (Cox–Mantel) test, so theoretically their results could be different from results estimated by a Cox PH model if the underlying hazard functions are not entirely proportional to each other, as suggested by Fig. 2 (4). The technique of estimating HR by reading KM curve directly performs well if there are a sufficient number of subjects and events and if the observation intervals are adequate (5), such as in that study.

On the third point, we wanted to avoid a laundry list of subgroup analysis of all possible scenarios; thus, we had chosen to focus our subgroup analysis on patient, tumor, and treatment characteristics that we believed matter the most in terms of their prognostic values. In addition, statistical theory has shown that estimation of HR and its validity does not depend on whether the study is done prospectively or retrospectively.

The numbers in Fig. 2 were slightly off from the original publications because of the algorithm used in RevMan software. RevMan computes a symmetric CI for log(HR) because they are supposed to be constructed based on a (symmetric) normal distribution. If the original CI reported is not perfectly symmetric (on a log scale), then there will be a slight discrepancy. Rounding can also contribute to this. Additional information can be found on the Revman manual for the statistical method and algorithm (6).

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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