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Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction *(J Natl Cancer Inst. 2015 Mar 18;107(5))*

Abstract
Background:
Previous studies have reported a breast cancer (BC) risk reduction of approximately 50% after risk-reducing salpingo-oophorectomy (RRSO) in BRCA1/2 mutation carriers, but may have been subject to several types of bias. The purpose of this nationwide cohort study was to assess potential bias in the estimated BC risk reduction after RRSO.

Methods:
We selected BRCA1/2 mutation carriers from an ongoing nationwide cohort study on Hereditary Breast and Ovarian Cancer in the Netherlands (HEBON). First, we replicated the analytical methods as previously applied in four major studies on BC risk after RRSO. Cox proportional hazards models were used to calculate hazard ratios and conditional logistic regression to calculate odds ratios. Secondly, we analyzed the data in a revised design in order to further minimize bias using an extended Cox model with RRSO as a time-dependent variable to calculate the hazard ratio. The most important differences between our approach and those of previous studies were the requirement of no history of cancer at the date of DNA diagnosis and the inclusion of person-time preceding RRSO.

Results:
Applying the four previously described analytical methods and the data of 551 to 934 BRCA1/2 mutation carriers with a median follow-up of 2.7 to 4.6 years, the odds ratio was 0.61 (95% confidence interval [CI] = 0.35 to 1.08), and the hazard ratios were 0.36 (95% CI = 0.25 to 0.53), 0.62 (95% CI = 0.39 to 0.99), and 0.49 (95% CI = 0.33 to 0.71), being similar to earlier findings. For the revised analysis, we included 822 BRCA1/2 mutation carriers. After a median follow-up period of 3.2 years, we obtained a hazard ratio of 1.09 (95% CI = 0.67 to 1.77).

Conclusion:
In previous studies, BC risk reduction after RRSO in BRCA1/2 mutation carriers may have been overestimated because of bias. Using a design that maximally eliminated bias, we found no evidence for a protective effect.