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RE: Breast Cancer Risk After Salpingo-Oophorectomy in Healthy *BRCA1/2* Mutation Carriers: Revisiting the Evidence for Risk Reduction

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Heemskerk-Gerritsen et al. (1) questioned the protective effect of risk-reducing salpingo-oophorectomy (RRSO) on breast cancer (BC) risk in women who carry a *BRCA1* or *BRCA2* (*BRCA1/2*) mutation, as previously reported. They proposed that studies addressing this question should ensure: 1) women are eligible only if they do not have breast or ovarian cancer and have both ovaries and breasts intact before DNA testing; 2) each woman is followed from the age of DNA testing; and 3) the time at risk considers RRSO as a time-dependent variable that takes value 0 before RRSO and 1 after. Using this design, their analysis of Hereditary Breast and Ovarian Cancer in the Netherlands (HEBON) data reported a BC hazard ratio (HR) by RRSO of 1.09 (95% confidence interval [CI] = 0.67 to 1.77). They hypothesized that the previously reported protective effect of RRSO on BC was because of failure to conform to one of these three design features.

Domchek et al. (2) and Kauff et al. (3) both have reported a protective effect of RRSO on BC for *BRCA1/2* mutation carriers (Table 1) in women followed prospectively from ascertainment with breasts and ovaries intact at start of follow-up. These analyses followed women who underwent RRSO from RRSO date. Therefore, these analyses did not conform to feature 2 above and may be subject to "immortal person-time bias." We updated the Prevention and Observation of Surgical Endpoints (PROSE) dataset reported by Domchek to accommodate additional subjects recruited since the original publication and current follow-up. We then reanalyzed the PROSE and Kauff data using RRSO as a time-dependent variable following each woman from the age at ascertainment, as per Wacholder et al. (4).

The hazard ratio estimates in the current reanalyses were similar to those previously reported (Table 1): RRSO conferred a protective effect on BC in both the PROSE and Kauff data. In PROSE, all BC cases occurred more than five months following RRSO. In Kauff, BC occurring less than six months after RRSO were excluded. Thus, as in the paper of Heemskerk-Gerritsen, it is doubtful that cases unlikely to be influenced by RRSO biased either analysis. Mavaddat et al. (5) also reported hazard ratio estimates for RRSO using the same approach as Heemskerk-Gerritsen and found hazard ratios of 0.52 (95% CI = 0.24 to 1.13) in *BRCA1* and 0.79 (95% CI = 0.35 to 1.80) in *BRCA2*.

In Figure 2, Heemskerk-Gerritsen et al. displayed cumulative BC risk by RRSO based on a "landmark" method (6). The x-axis of this figure started from age 30 years and risk started to increase at about age 31 years, implying the "landmark time" used was approximately 31 years. As the minimum age at RRSO in HEBON was 31 years, it is likely the estimated curve of the RRSO group was unstable when the number of carriers undergoing RRSO was small at the beginning of the curve. Choice of landmark time can clearly have large impact on the graphical display of the RRSO protective effect (6). It is not clear how the figure would appear if a different landmark time were used. Finally, if RRSO effects depend on age, then the difference in censoring events in HEBON vs the PROSE or Kauff data may lead to different effect estimates.

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Table 1. Hazard ratio estimates of RRSO for breast cancer from the prospective cohort studies by Domchek et al. (2) and Kauff et al. (3) among *BRCA1/2* carrier women without prior breast or ovarian cancer and without prior RRSO/RRM

Study	*BRCA1*	*BRCA2*	*BRCA1/2*
Domchek et al. (2010), No. (%)	(n = 970)	(n = 597)	(n = 1567)
RRSO			
Yes	294 (30.3)	155 (26.0)	449 (28.7)
Cancer	40 (13.6)	13 (8.4)	53 (11.8)
No	676 (69.7)	442 (74.0)	1118 (71.3)
Cancer	137 (20.3)	96 (21.7)	233 (20.8)
HR estimates (95% CI) and *P* value using the approach of Heemskerk-Gerritsen (1)*	0.63 (0.42 to 0.93)* *P* = .021	0.40 (0.19 to 0.84)* *P* = .015	0.59 (0.42 to 0.82)* *P* = .001
HR estimates (95% CI) and *P* value using Domchek (2) original approach†	0.56 (0.39 to 0.81)* *P* = .002	0.42 (0.21 to 0.86)* *P* = .02	0.51 (0.36 to 0.70)* *P* = .001
Kauff et al. (2008), No. (%)	(n = 220)	(n = 125)	(n = 345)
RRSO			
Yes	100 (45.5)	60 (48)	160 (46.4)
Cancer	6 (6)	2 (3.3)	8 (5)
No	120 (54.5)	65 (52)	185 (53.6)
Cancer	11 (9.2)	5 (7.7)	16 (8.6)
HR estimates (95% CI) and *P* value using the approach of Heemskerk-Gerritsen (1)‡	0.47 (0.16 to 1.37) *P* = .17	0.47 (0.06 to 3.86) *P* = .49	0.50 (0.20 to 1.25) *P* = .14
Original HR estimates (95% CI) and *P* value in Kauff (3)	0.61 (0.30 to 1.22) *P* = .16	0.28 (0.08 to 0.92) *P* = .036	0.53 (0.29 to 0.96) *P* = .036

* Age was used as the time scale with left truncation at the age of ascertainment in the Cox regression analyses. RRSO was used as a time-dependent variable that took value 0 before and 1 after RRSO. We stratified on study center and accounted for family correlation using robust variance estimates (7). All analyses adjusted for year of birth (<1940, 1940–49, 1950–59, 1960–69, ≥1970), parity (yes or no), and, in the analyses of combined carrier group, mutation status (*BRCA1* or *BRCA2*). For *BRCA2*, year of birth was adjusted as whether born before 1960 or not. RRSO = risk-reducing salpingo-oophorectomy.

† This analysis used the same approach as Domchek et al. (2010). Time since age of RRSO was used for RRSO users, and time since ascertainment was used for non-RRSO users as time scale in Cox regression analyses. We stratified on study center and accounted for family correlation using robust variance estimates (7). All analyses adjusted for year of birth (whether born before 1960 or not).

‡ The analysis was the same as in the first note, except that follow-up started from age at genetic testing. Parity (yes or no) was adjusted for *BRCA1*, history of prior use of hormone replacement therapy (yes or no) for *BRCA2*, and both for the combined carrier group in addition to the mutation status.