

What Have We Learned from Risk-Reducing Salpingo-oophorectomy?

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In this issue of the Journal, Rebbeck et al. (1) have provided us with a meticulously executed, up-to-date meta-analysis that quantifies the reductions in the risks of breast and ovarian/fallopian tube cancer that follow risk-reducing salpingo-oophorectomy (RRSO) in *BRCA1* and *BRCA2* (*BRCA1/2*) mutation carriers. Their conclusion—“The summary risk reduction estimates presented here indicate that RRSO is strongly associated with reductions in the risk of breast and ovarian/fallopian cancers, and should provide guidance to women in planning cancer risk reduction strategies”—is fully supported by their analysis and will not surprise those who have followed the rapidly evolving management strategies for *BRCA1/2* mutation carriers.

From our perspective, four features commend this study. First, the meta-analysis that forms the basis of these conclusions was carefully designed and thoughtfully implemented. The authors identified and included all relevant publications, used state-of-the-art statistical methods, excluded reports with overlapping study populations, evaluated potential interstudy heterogeneity, and tested for publication bias. Importantly, Rebbeck et al. attempted to disentangle potential differences between *BRCA1* and *BRCA2* mutation carriers who, despite having superficial similarities with regard to phenotype, have important biological differences that render a combined analysis suboptimal. Consequently, one can have confidence in their findings, particularly because they detected no evidence of heterogeneity in effect size among the 10 pooled studies, despite substantial heterogeneity in study designs. The lack of statistical heterogeneity provides considerable reassurance that the pooled estimates are accurate.

The second valuable report feature, therefore, is its provision of improved breast and ovarian/fallopian tube cancer risk reduction estimates, to better inform the patient and provider about RRSO-related decision making. The meta-analysis gave point estimates of risk that are more precise and 95% confidence intervals surrounding those estimates that are substantially narrower than those based on any of the individual studies. For example, when viewed separately, the published studies are consistent with as much as an 85% (the lowest 95% confidence interval boundary) reduction in breast cancer risk in *BRCA1* mutation carriers and up to a 22% (the highest 95% confidence interval boundary) increase in risk [table 2 in Rebbeck et al. (1)]. Although there is no biological basis for anticipating an increase in breast cancer risk after RRSO, studies in which the 95% confidence interval includes 1.0 are statistically compatible with no risk reduction. When the studies were pooled, the range became much tighter—from as much as a 65% reduction in risk to as little as a 36% reduction in risk—and the 95% confidence interval no longer included 1.0. The pooled point estimate (51% breast cancer risk reduction in *BRCA1* mutation

carriers) represents improved precision relative to the individual studies.

Emerging data regarding the adverse consequences of ambiguity [“uncertainty regarding the reliability, credibility or adequacy of information about risks and the potential outcomes of decisions” (2)] related to medical information provided to patients—for example, lower colon, lung, and skin cancer screening uptake in a cross-sectional study (2) and reduced mammographic screening uptake in a prospective study (3)—suggest that this improved precision should benefit women who are trying to decide whether or not to undergo RRSO. We urge providers of cancer genetics counseling services to adopt the summary risk estimates developed by Rebbeck et al. as those most currently reliable when counseling *BRCA* mutation carriers.

Third, the authors’ detailed discussion of their study limitations and the related literature provides an excellent outline of future research topics, including improved estimates of: 1) breast cancer risk reduction in *BRCA2* carriers; 2) ovarian cancer risk reduction related to both genes; 3) optimal timing (age) for RRSO; 4) impact of age-at-RRSO on subsequent cancer risk; 5) post-RRSO risk of primary peritoneal cancer (now that bilateral salpingectomy is a risk-reducing surgery component); and 6) nononcological risks related to surgical menopause.

Finally, the article by Rebbeck et al. provides an opportunity to reflect on what we have learned from introducing “prophylactic oophorectomy” into the management of women whose families have multiple cases of breast or ovarian cancer, a practice which long predated the discovery of *BRCA1/2*. It was not so long ago that removing “healthy” ovaries from such women was viewed as an outrageous notion, one that was met with widespread resistance by physicians from diverse specialties. And when this surgery was performed, the potential importance of the fallopian tubes was neglected. In the past, many women were treated with oophorectomy alone, and their fallopian tubes were left intact. In retrospect, malignant transformation within fallopian tube mucosa may have accounted for at least a fraction of “primary peritoneal carcinoma,” an ovarian cancer-like illness initially observed in oophorectomized

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women from high-risk families (4). Gradually, the appropriateness of surgical risk reduction gained wider acceptance, facilitated by the discoveries of *BRCA1/2* mutations and the ability to identify the specific members of mutation-positive families upon whom intervention strategies should be focused.

Subsequently, we learned that the fallopian tube was a target organ at risk of malignant transformation in *BRCA* mutation carriers (5), which led to incorporation of bilateral salpingectomy into surgical risk reduction strategies. Today, it would be unthinkable to leave the fallopian tubes in place at the time of risk-reducing oophorectomy. The opening of the National Ovarian Cancer Prevention and Early Detection Study (Gynecologic Oncology Group protocol 199) at 150 study sites across the United States and Australia, with its protocol-based recommendation supporting RRSO and standardized tissue processing protocol (including pathology review of serial 2-mm sections from both ovaries and fallopian tubes) (6), fostered adoption of these strategies in communities that had been reluctant to move in this direction.

The inability to identify a consistent, reproducible precursor lesion in the high-risk ovaries from *BRCA* mutation carriers triggered a search for alternative ovarian cancer pathogenesis hypotheses (7). As the number of RRSO procedures increased, and frequent meticulous histopathologic review of the entire RRSO surgical specimen became the standard of care, the prevalence of clinically occult fallopian tube neoplasms detected—ranging from mild epithelial atypia to carcinoma in situ to invasive carcinomas—steadily increased. This recognition that fallopian tube cancers represent the majority of clinically occult malignancies identified in RRSO specimens led to a novel hypothesis of pelvic serous cancer pathogenesis, which posits that a substantial proportion of what has previously been classified as “ovarian cancer” may, in fact, be carcinoma of fallopian tube origin (8), an observation that may profoundly alter the paradigms related to ovarian cancer etiology and management.

Finally, discovering that RRSO is also associated with a large reduction in *BRCA* mutation-related breast cancer risk, particularly among women who are premenopausal at RRSO (1,9), has made this surgical intervention much more acceptable to high-risk women. Thus, RRSO has not only resulted in substantial reductions

in cancer incidence and perhaps mortality (10) among *BRCA* mutation carriers but also catalyzed major advances in our understanding of ovarian carcinogenesis. The more accurate post-RRSO cancer risk estimates provided by Rebbeck et al. constitute another important improvement in the management of high-risk women.

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