

EDITORIAL COMMENT

Is Preventative Oophorectomy Safe?

Providing Reassurance to Young Women at Risk



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Women carrying germline pathogenic variants in the *BRCA1* or *BRCA2* genes have a markedly increased risk of developing ovarian cancer during their lifetime. In a contemporary prospective cohort study that included 9,856 patients with *BRCA1/2* pathogenic variants, the cumulative ovarian cancer risk by age 80 years was 44% for *BRCA1* carriers and 17% for *BRCA2* carriers.¹ Risk-reducing salpingo-oophorectomy (RRSO) is highly effective for prevention, reducing the risk of ovarian cancer by at least 80%,² and is currently recommended between the ages of 35 and 40 years for *BRCA1* carriers and between ages 40 and 45 years for *BRCA2* carriers.³ However, RRSO inevitably leads to premature menopause, and the abrupt decline in estrogen can be associated with a number of acute symptoms including hot flashes, sexual dysfunction, insomnia, and mood disturbances.^{4,5} Additionally, it is generally the potential long-term effects of premature menopause that raise the most concerns for young women undergoing RRSO, given they face decades of increased risk for osteoporosis, cardiovascular disease (CVD), and other comorbidities in the context of their longer life expectancies.⁶

The impact of RRSO on cardiovascular health in particular has not been well-studied, despite being a frequently encountered concern in clinical practice. Studies including large meta-analyses have demonstrated a greater risk of coronary heart disease, heart failure, cardiovascular mortality, and other CVD with premature *natural* menopause,⁷⁻⁹ but whether these same risks are associated with premature *iatrogenic*

menopause due to RRSO is less certain. In the paper that accompanies this editorial, Beekman et al¹⁰ evaluated whether premature menopause due to RRSO is associated with development of coronary artery calcium (CAC), a well-established marker for elevated CVD risk. The 328 patients included in this analysis were derived from a nested, cross-sectional study of women at high familial risk for breast and/or ovarian cancer who had undergone RRSO.¹¹ The investigators compared CAC scores between patients aged 60 to 70 years at study enrollment who had undergone a RRSO while still premenopausal (≤ 45 years) vs those who had undergone a RRSO after natural menopause (≥ 54 years). Importantly, there were no significant differences in increased CAC scores, measured using the standardized Agatston method, between premenopausal and postmenopausal RRSO groups after adjustment for age, hypertension, and dyslipidemia (relative risk [RR]: 0.93; 95% CI: 0.75-1.15 for any CAC [CAC >0]; RR: 0.71; 95% CI: 0.43-1.17 for at least moderate CAC [CAC >100]; RR: 0.81; 95% CI: 0.30-2.13 for severe CAC [CAC >400]).

In asymptomatic patients without established atherosclerotic CVD, CAC is a validated measure of subclinical atherosclerosis burden and future risk of CVD.¹²⁻¹⁵ In addition, a recent study by Chu et al¹⁶ demonstrated CAC to be predictive of atherosclerotic CVD events in women who had experienced premature natural menopause, specifically. Like Beekman et al,¹⁰ Chu et al¹⁶ found a similar distribution of CAC scores between women with and without premature menopause, yet women with premature menopause nonetheless had a significantly higher risk for atherosclerotic CVD events at 15-year follow-up. This may relate to some of the known limitations of CAC scoring in quantifying CVD risk, given that this single measure does not capture other potentially important etiologies of CVD risk including noncalcified plaques, microvascular coronary disease, or atherosclerotic disease in other vascular beds, all of

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which increase the risk of CVD events.¹⁷ Additionally, these alternative pathways for increased CVD may more commonly occur in women^{18,19} and thus underscore a significant limitation in using CAC as a sole marker for CVD risk in this patient population. As the investigators acknowledge, the study was subject to survival bias, unable to enroll those individuals with the most advanced CVD who died from cardiovascular events, although this accounted for only 1.9% of the eligible population. The study also excluded individuals who had undergone coronary stent procedures, again potentially limiting inclusion of those with most advanced CVD. It is important to note that whereas premenopausal RRSO patients had similar CAC scores to matched control subjects in an external reference cohort, they had significantly higher median body mass index (27.2 kg/m² vs 25.4 kg/m²; $P < 0.001$) and a higher prevalence of diabetes mellitus (6.3% vs 2.8%; $P < 0.001$). Although Beekman et al¹⁰ appropriately controlled for CVD risk factors in all analyses, the presence of these comorbidities warrants equal attention when considering the overall impact of RRSO on the long-term health of young women with *BRCA1/2* pathogenic variants.

The results of this analysis conflict with prior evidence suggesting a higher risk of CVD after surgical menopause than with natural menopause.²⁰ However, in the previous studies, surgery was often performed at later ages than what is currently recommended for *BRCA1/2* carriers undergoing RRSO. To this end, the investigators also examined timing of premenopausal RRSO, identifying no detrimental effect of pursuing early (<41 years) vs late (41-45 years) premenopausal RRSO on subsequent CAC scores. The investigators postulate that it is not premature menopause that causes an elevated risk of CVD, but rather that accelerated vascular aging—which could result in earlier natural menopause—may be the culprit; as a result, premature surgical menopause was not associated with increased CAC scores in this cohort. Another possibility is that increased health care utilization by *BRCA1/2* carriers, women who have interacted with the health care system to identify their gene mutation, may lead to earlier intervention of modifiable CVD risk factors. Moreover, the health care system in the Netherlands ranks very favorably compared to other developed countries, and access to effective preventive care may have impacted outcomes in this cohort.²¹

Reflective of the high lifetime risk of developing breast cancer associated with *BRCA1/2* mutations, 60% of patients in this study had a personal history of

breast cancer. Additional challenges arise when caring for these patients, given that treatments for breast cancer, including chemotherapy, endocrine therapy, and ovarian function suppression (OFS), can also cause menopausal symptoms. Yet hormone replacement therapy (HRT), which may be used to lessen such symptoms after RRSO, is contraindicated in breast cancer survivors due to the potential increased risk for recurrence. However, no protective effect from HRT on CAC scores was observed in this study, despite older studies suggesting that HRT could reduce the risk of coronary heart disease after premature surgical menopause.^{22,23} With OFS now widely used to treat premenopausal hormone-sensitive breast cancer in the wake of the seminal Suppression of Ovarian Function Trial,²⁴ Beekman et al's findings¹⁰ may additionally provide some reassurance for young women with breast cancer being considered for gonadotropin-releasing hormone agonists or other interventions to induce OFS.

In view of the significant physical and psychosocial impact that premature menopause can have on premenopausal women, it is crucial that a variety of factors be considered when timing RRSO in patients with *BRCA1/2* pathogenic variants, including individual cancer recurrence risk, symptomatology, comorbidities, reproductive goals, social and financial factors, and patient preference. Acknowledging the aforementioned limitations of CAC scoring, the study reported by Beekman et al¹⁰ in this issue of *JACC: CardioOncology* provides valuable new data to support informed decision-making when counselling *BRCA1/2* carriers on future CVD risk secondary to RRSO. Longer-term data from this cohort evaluating hard CVD outcomes such as incidence rates of coronary heart disease will be helpful in determining true CVD risk in patients with premature iatrogenic menopause. For the time being, multidisciplinary care between oncologists, primary care providers, geneticists, and cardiologists remains imperative when caring for patients undergoing RRSO, in order to optimize prevention and management of modifiable risk factors for CVD.

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