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HRT and Breast Cancer Risk After RRSO in BRCA1/2 Carriers: A Systematic Review and Meta-Analysis

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Abstract

Background

Risk-reducing bilateral salpingo-oophorectomy (RRSO) reduces ovarian cancer risk in BRCA1/2 carriers but causes premature menopause. Hormone replacement therapy (HRT) can mitigate its consequences, yet concerns regarding breast cancer risk remain an important barrier to its use. Evidence is limited, particularly regarding formulation-specific risks.

Methods

A systematic review and meta-analysis was conducted according to PRISMA guidance using a protocol registered in PROSPERO CRD420261378792. Major electronic databases were searched for observational studies evaluating breast cancer outcomes following RRSO/RRBO. Adjusted hazard ratios were prioritized. Random-effects models using restricted maximum likelihood estimation with Hartung–Knapp adjustment were applied, with heterogeneity assessed using I^2 and Cochran's Q. Separate analyses were performed for any HRT, estrogen-only therapy, and combined estrogen–progestogen therapy. Sensitivity analyses were conducted to assess study influence and alternative effect measures.

Results

Four studies contributed to the preliminary quantitative synthesis. Any HRT was associated with a pooled HR of 0.48 (95% CI, 0.23–0.98; I^2 = 0%). Estrogen-only therapy yielded 0.56 (95% CI, 0.002–145.78; I^2 = 81.1%), while combined estrogen–progestogen therapy yielded 1.01 (95% CI, 0.48–2.14; I^2 = 0%). An exploratory sensitivity analysis using event-level data from five studies yielded a pooled OR of 0.58 (95% CI, 0.46–0.73; I^2 = 0%), incorporating both adjusted and crude estimates.

Conclusion

Preliminary findings suggest that the association between HRT and breast cancer risk in BRCA1/2 carriers may differ by formulation, but the small number of available studies and substantial uncertainty in some estimates preclude definitive conclusions. This systematic review and meta-analysis will provide a rigorous, contemporary synthesis of the evidence following RRSO/RRBO, distinguish findings by HRT formulation, and transparently assess heterogeneity and study limitations. The results may strengthen evidence-based counseling and shared decision-making regarding menopausal hormone therapy in BRCA1/2 carriers, while identifying critical gaps in the literature and priorities for future prospective research.

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