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Review Article

Managing hereditary breast cancer risk in women with and without ovarian cancer

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HIGHLIGHTS

- Most women with ovarian cancer use genetic testing that informs breast cancer risk
- For BRCA1/2 carriers, breast cancer screening depends on ovarian cancer prognosis
- For early-stage or favorable advanced stage, screening is reasonable
- For unfavorable advanced stage, screening is appropriate if disease-free 2 years
- Prophylactic mastectomy can be considered for carriers in remission after 5 years

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ABSTRACT

Current guidelines recommend that all women with ovarian cancer undergo germline genetic testing for *BRCA1/2*. Increasingly, genetic testing is being performed via panels that include other genes that confer a high or moderate risk of breast cancer. In addition, many women with a family history of breast or ovarian cancer are not found to have a mutation, but may have increased risk of breast cancer for which surveillance and risk reduction strategies are indicated. This review discusses how to assess and manage an increased risk of breast cancer through surveillance, preventive medications, and risk-reducing surgery.

Assessing and managing the increased risk of breast cancer in *BRCA1/2* mutation carriers after a diagnosis of ovarian cancer can be challenging. For the first few years after an ovarian cancer diagnosis, *BRCA1/2* mutation carriers have a relatively low risk of breast cancer, and their prognosis is largely determined by the ovarian cancer. However, if these women remain in remission after two years, the risk of breast cancer becomes comparable with, and in some cases exceeds, their risk of ovarian cancer recurrence. For these women, breast cancer surveillance and risk reduction becomes important to their overall health.

Specifically, for *BRCA1/2* carriers who are diagnosed with early-stage ovarian cancer, we recommend regular breast cancer surveillance and consideration of risk reduction with medication and/or prophylactic mastectomy. For women with advanced ovarian cancer who do not achieve remission, breast cancer surveillance or prophylaxis is not of value. However, among carriers with more favorable advanced disease, it is reasonable to initiate breast cancer surveillance. Patients with less favorable advanced stage disease who achieve sustained remission (>2–5 years) should also consider more aggressive strategies for breast cancer screening and prevention. For mutation carriers who remain in remission after five years, prophylactic mastectomy can be considered.

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Epidemiologic studies have demonstrated that 14.1% of women with non-mucinous ovarian cancer and 22.6% of women with high-grade serous ovarian cancer have a germline *BRCA1* or *BRCA2* (*BRCA1/2*) mutation. Of these, 44% have no family history [1]. Based on these data, the National Comprehensive Cancer Network (NCCN) now recommends that all women with ovarian cancer be tested for germline mutations in *BRCA1* and *BRCA2* [2]. Next generation sequencing panels that assess mutations in many cancer susceptibility genes simultaneously are now in wide use. As a result, many other inherited mutations that confer a moderate risk of developing breast and ovarian cancer are now being identified. The goal of this review is to discuss how to manage women with an increased risk of breast cancer, including those with hereditary breast cancer risk, through screening, preventive medications, and risk-reducing surgery. In addition, we will discuss how to assess and manage the increased risk of breast cancer in *BRCA1/2* mutation carriers after a diagnosis of ovarian cancer.

1. Genetic testing for hereditary breast cancer

There are a number of identified high-risk breast cancer susceptibility genes, including *BRCA1*, *BRCA2*, *PALB2*, *TP53*, *CDH1*, and *PTEN*. The cumulative breast cancer risk associated with mutations in these genes is at least 5-fold the population risk. Mutations in moderate-risk breast cancer susceptibility genes have also been identified and confer a two- to five-fold increased breast cancer risk, with *ATM* and *CHEK2* mutations most common [3]. Several other candidate moderate-risk breast cancer susceptibility genes have been proposed. We are in a period in which the specific cancer risks associated with mutations in these genes are still being fully defined. It is notable that three of the genes on most panels are ovarian cancer susceptibility genes, *BRIP1* [4], *RAD51C* [5] and *RAD51D* [5] that may not be associated with breast cancer risk. The overall lifetime risks of breast and ovarian cancers associated with mutations in each susceptibility gene are shown in Table 1.

Table 1
Breast cancer risk susceptibility genes.[a]

	Lifetime breast cancer risk (age 80)[b]	Lifetime ovarian cancer risk	References
BRCA1	67%–75% RR 11.4	45%	[3,81]
BRCA2	66%–76% RR 11.7	12%	[3,81]
Genes other than *BRCA1/2*: high risk			
CDH1	53% RR 6.6 (2.2–19.9)	No increase	[3]
PALB2	45% RR 5.3 (3.0–9.4)	OR 2.3–10.2 Inconsistent data	[3,12,82]
PTEN	RR 25–39[d]	No increase	[3]
TP53	RR 105 (62–165)	Risk increased for many cancers. No specific risk estimate for ovarian cancer	[3]
Moderate risk			
ATM	27% RR 2.8 (2.2–3.7)	No increase	[3]
CHEK2	20–29% RR 2.3–3.0	No increase	[3,13,83]
NBN[c]	23% RR 2.7 (1.9–3.7)	No increase	[3]
STK11	31–45%[e]	RR 27[f]	[3,84]
Average risk			
BRIP1	No increase	4.1–12.7% RR 3.4–11.2	[4,82]
RAD51C	No increase	6.1% OR 5.2	[5]
RAD51D	No increase	13.6% OR 12	[5]

RR: relative risk; OR: odds ratio.
[a] BARD1 not included since breast and ovarian cancer risk estimates are inconsistent [3,4,82].
[b] Risks higher in those with significant breast cancer family history; 95% confidence interval reported for RR in parenthesis when single RR reported.
[c] Risk estimate based on one mutation: c.657del5.
[d] Based on population with Cowden syndrome, which may overestimate risk.
[e] May be an overestimate due to ascertainment from Peutz-Jeghers syndrome cohorts.
[f] Sex-cord tumors (no increase in epithelial ovarian cancer).

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