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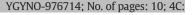
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Managing hereditary breast cancer risk in women with and without ovarian cancer

Mary Linton Peters ^{a,*}, Judy E. Garber ^b, Nadine Tung ^a

^a Division of Hematology-Oncology, Beth Israel Deaconess Medical Center, Boston, MA, United States
^b Center for Cancer Genetics and Prevention, Dana-Farber Cancer Institute, Boston, MA, United States

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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* Corresponding author at: Division of Hematology-Oncology, Beth Israel Deaconess Medical Center, 330 Brookline Ave, RW4-T1, Boston, MA 02215, United States. *E-mail address*: mbpeters@bidmc.harvard.edu (M.L. Peters).

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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 riskreducing 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.

Table 1

Breast cancer risk susceptibility genes.^a

Lifetime breast cancer risk (age 80)^b Lifetime ovarian cancer risk References BRCA1 67%-75% 45% [3,81] RR 114 BRCA2 66%-76% 12% [3,81] RR 117 Genes other than BRCA1/2: high risk CDH1 53% No increase [3] RR 6.6 (2.2-19.9) OR 2.3-10.2 [3,12,82] PALB2 45% RR 5.3 (3.0-9.4) Inconsistent data PTEN RR 25-39d No increase [3] RR 105 (62-165) [3] TP53 Risk increased for many cancers. No specific risk estimate for ovarian cancer Moderate risk 27% No increase [3] ATM RR 2.8 (2.2-3.7) CHEK2 20-29% No increase [3,13,83] RR 2.3-3.0 NRN 23% No increase [3] RR 2.7 (1.9-3.7) 31-45%^e RR 27^f STK11 [3,84] Average risk **BRIP1** No increase 41-127% [4.82] RR 3.4-11.2 RAD51C No increase 6.1% [5] OR 5.2 RAD51D No increase 13.6% [5] OR 12

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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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 twoto 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. Download English Version:

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