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Breast Cancer Surgical Risk Reduction for Patients With Inherited Mutations in Moderate Penetrance Genes

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Improvements in sequencing technology and multigene panel testing have helped identify a growing number of patients with mutations in *moderate penetrance genes*,[1,2] defined as genes associated with a relative risk (RR) of breast cancer that is 2 to 5 times higher than population risk.[1,3] These mutations increase primary breast cancer risk by a magnitude similar to the risk associated with atypical ductal or lobular hyperplasias,[3] yet little data are available to define the magnitude of the risk of contralateral breast cancer (CBC) in affected individuals. The breast oncology community is faced with counseling patients regarding the advantages and disadvantages of risk-reducing strategies based on scant data. In this article, we summarize the available information on the risk of primary breast cancer and CBC associated with moderate penetrance genes to facilitate surgical risk-reduction counseling.

Risk Estimates

We selected 2 publications, a meta-analysis by Easton et al[4] and a specimen-based case-control study by Couch et al,[2] that provide a comprehensive analysis of the most commonly discussed moderate penetrance genes. The use of various methodologies explains the differences in the reported risk values.

Primary Breast Cancer

Mutations in *BRCA1/2* are high-risk germline mutations and confer an increased RR of breast cancer of 11.4 (for *BRCA1* [OMIM 113705] carriers) and 11.7 (for *BRCA2* [OMIM 600185] carriers),[4] an absolute lifetime risk of 72% (*BRCA1*) and 69% (*BRCA2*) by age 80 years.[5] Patients with a pathogenic *PALB2* (OMIM 610335) mutation have an RR of breast cancer that is approximately 6 times higher than population risk,[2,4] which translates into a lifetime risk of 45%.[4] Pathogenic mutations in *CDH1* (OMIM 192090, associated with diffuse gastric cancer and lobular breast carcinoma) confer an RR that is 6.6-fold higher than population risk (90% CI, 2.2-19.9), for a lifetime risk of 53%.[4] Patients with Li-Fraumeni syndrome (*TP53* [OMIM 151623] mutation) also have an elevated risk of breast cancer, but studies in this population are fraught with ascertainment bias, making precise risk estimation difficult.[4]

Mutations associated with somewhat lower risks include pathogenic mutations in *ATM* (OMIM 607585) or truncating *CHEK2* (OMIM 604373) mutations (eg, c.1100delC), which confer an increased risk of breast cancer that is 3 times higher than the population risk.[2,4] The breast cancer risk associated with pathogenic mutations in *NBN* (OMIM 602667) and *NF1* (OMIM 162200) are reported to be around 2 times greater than the population risk, but these estimates are based on small numbers and are not consistent between reports. Couch et al[2] also found an increased risk associated with *BARD1* (OMIM 601593) and *RAD51D* (OMIM 602954) mutations, despite analyses that report otherwise.[3] Mutations in *PTEN* (OMIM 601728; Cowden syndrome) and *STK11* (OMIM 602216; Peutz-Jeghers syndrome) confer an elevated RR of breast cancer (39.1 [90% CI, 26.7-54.9]; and 45% [95% CI, 29%-64%] by age 70 years; respectively); but like the risk estimates for patients with Li-Fraumeni syndrome, this risk may have been overestimated because of ascertainment bias[4] and so risk estimates are not stable.

Table. Germline Mutations and Their Associated Primary Breast Cancer Risk

Mutation	Easton et al,[4] 2015, Meta-analysis RR (90% CI)	Couch et al,[2] 2017, Case-Control OR (95% CI)
BRCA1	11.4 (NR)	NS
BRCA2	11.7 (NR)	NS
PALB2	5.3 (3.0-9.4)	7.46 (5.12-11.19)
CDH1	6.6 (2.2-19.9)	NS
TP53	105 (62-165)	NS
ATM	2.8 (2.2-3.7)	2.78 (2.22-3.62)
CHEK2 truncating	3.0 (2.6-3.5)	2.31 (1.88-2.85)
NF1	2.6 (2.1-3.2)	0.94 (0.55-1.62)
NBN	2.7 (1.9-3.7)	1.13 (0.73-1.75)
BARD1	NS	2.16 (1.31-3.63)
RAD51D	NS	3.07 (1.21-7.88)
PTEN	NSE	NS
STK11	NSE	NS
CHEK2 missense	NS	1.48 (1.31-1.67)
RAD50	NS	0.77 (0.52-1.61)
RAD51C	NS	0.78 (0.47-1.37)
MRE11A	NS	0.86 (0.46-1.57)
CDKN2A	NS	2.47 (0.83-8.16)
MSH2	NS	2.46 (0.81-6.93)
MSH6	NS	1.93 (1.16-3.27)
MLH1	NS	1.15 (0.30-4.19)
PMS2	NS	0.82 (0.44-1.47)

Abbreviations: NR, not reported; NS, not studied; NSE, no stable estimate for risk (although risk is known to be elevated in patients with mutations in *PTEN* and *STK11*); OR, odds ratio; RR, relative risk.

Missense *CHEK2* mutations (p.Ile157Thr and p.Ser428Phe in Couch et al[2] and pIle157Thr only in Easton et al[4]) are associated with a slightly elevated RR of breast cancer of 1.3; their clinical significance is controversial. Sufficient evidence to estimate breast cancer risks for other genes frequently included on multigene panels (eg, *RAD50*, *MRE11A*, *RECQL*, *RINT1*) is lacking.[3] Finally, germline mutations in the genes associated with Lynch syndrome (ie, *MSH2, MSH6, MLH1, PMS2*) are not generally associated with higher risk of breast cancer (**Table**).

Risk of Contralateral Breast Cancer

CBC risk among *BRCA* mutation carriers is well defined, approaching 40% for *BRCA1* carriers and 30% for *BRCA2* carriers at 20 years

after their primary breast cancer.[5] Data are limited on the risk of CBC in affected patients with mutations in moderate penetrance genes. Patients with a truncating *CHEK2* mutation (c.1100delC) appear to have an RR of CBC of 2.77, although follow-up is limited (median follow-up, 6.6 years).[6] Currently, no data are available that estimate the risk of CBC for patients with mutations in the remaining moderate penetrance genes. Models of germline genetic cancer predisposition would imply increased CBC risk; however, even in large series from commercial laboratories,[2] the number of carriers is small and follow-up is limited, making accurate risk assessment difficult.

Recommendations

Patients with a *BRCA1/2* mutation have an approximately 70% lifetime risk of breast cancer,[5] and the role of surgical risk reduction is well defined. *PALB2* is now considered high risk by many because germline mutations in *PALB2* confer an RR of breast cancer more than 5-fold. For these high-risk germline mutations, including *BRCA1*, *BRCA2*, *PALB2*, *CDH1*, and *TP53*, we recommend NCCN guidelines-based high-risk screening, consider surgical prophylaxis. Radiation-induced secondary malignant neoplasms are a concern for patients with a *TP53* mutation (Li Fraumeni syndrome); thus, mastectomy is often favored over lumpectomy. Outcomes of bilateral prophylactic mastectomy in patients with germline mutations in moderate penetrance genes are not available; however, surgical risk reduction is generally not encouraged for the level of risk imparted by these mutations (2- to 5-fold), so we recommend NCCN guidelines-based high-risk screening for breast cancer. The increased risk associated with these mutations resembles the risk of atypical ductal and lobular hyperplasia (RR, 4.24; 95% CI, 3.26-5.41),[7] for which bilateral prophylactic mastectomy is discussed yet rarely pursued. This knowledge should be kept in mind when counseling a patient with a similar magnitude of breast cancer risk resulting from a germline mutation in a moderate penetrance gene. No change in practice for breast cancer is recommended on the basis of genetic mutations with less than a 2-fold RR of breast cancer (*CHEK2* missense, *RAD50*, *RAD51C*, *MRE11A*, *CDKN2A*, *MSH2*, *MSH6*, *MLH1*, *PMS2*) until more evidence is available. Patients should be screened appropriately for the correlating cancer risk (eg, colon). Tung et al[3] provide guidance on management strategies, including high-risk screening and surgery, for carriers of moderate penetrance gene mutations.

Contralateral prophylactic mastectomy in affected *BRCA1/2* mutation carriers reduces the risk of a second breast cancer event by 90%. In the absence of definitive data regarding CBC risk in patients with moderate penetrance gene mutations, discussions regarding the potential benefits of contralateral surgical risk reduction should include considerations of the index tumor biology (ie, hormone receptor positive or negative) and potential impact of systemic therapy on reducing risk of CBC. The decision to pursue contralateral prophylactic mastectomy remains an individualized decision for patients with moderate penetrance gene mutations. Breast surgeons play an important role in the decision-making process and have a responsibility to ensure that patients are making informed choices.

Conclusions

As the indications for panel testing evolve, more confident risk estimates are expected to become available.[1] Until then, managing patients with mutations in moderate penetrance genes will remain a clinical challenge. When discussing personalized risk management strategies, surgeons should convey that germline mutations in most moderate penetrance genes are associated with an increased primary breast cancer risk of the same magnitude as the risk associated with atypical ductal or lobular hyperplasia and that no definitive data exist on the magnitude of CBC risk. Although it remains an individualized decision, surgical risk reduction is generally not encouraged.

ARTICLE INFORMATION

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REFERENCES

1. Desmond A, Kurian AW, Gabree M, et al. Clinical actionability of multigene panel testing for hereditary breast and ovarian cancer risk assessment. *JAMA Oncol*. 2015;1(7):943-951. doi:10.1001/jamaoncol.2015.2690

2. Couch FJ, Shimelis H, Hu C, et al. Associations between cancer predisposition testing panel genes and breast cancer. *JAMA Oncol*. 2017;3(9):1190-1196. doi:10.1001/jamaoncol.2017.0424

3. Tung N, Domchek SM, Stadler Z, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. *Nat Rev Clin Oncol*. 2016;13(9):581-588. doi:10.1038/nrclinonc.2016.90

4. Easton DF, Pharoah PD, Antoniou AC, et al. Gene-panel sequencing and the prediction of breast-cancer risk. *N Engl J Med*. 2015;372(23):2243-2257. doi:10.1056/NEJMsr1501341

5. Kuchenbaecker KB, Hopper JL, Barnes DR, et al; BRCA1 and BRCA2 Cohort Consortium. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA*. 2017;317(23):2402-2416. doi:10.1001/jama.2017.7112

6. Weischer M, Nordestgaard BG, Pharoah P, et al. CHEK2*1100delC heterozygosity in women with breast cancer associated with early death, breast cancer-specific death, and increased risk of a second breast cancer. *J Clin Oncol*. 2012;30(35):4308-4316. doi:10.1200/JCO.2012.42.7336

7. Hartmann LC, Sellers TA, Frost MH, et al. Benign breast disease and the risk of breast cancer. *N Engl J Med*. 2005;353(3):229-237. doi:10.1056/NEJMoa044383