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Two Decades After *BRCA:* Setting Paradigms in Personalized Cancer Care and Prevention

Fergus J. Couch[1,*], **Katherine L. Nathanson**[2], and **Kenneth Offit**[3]

[1]Division of Experimental Pathology and Laboratory Medicine, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN 55905, USA.

[2]Division of Translational Medicine and Human Genetics, Department of Medicine, Abramson Cancer Center, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.

[3]Clinical Genetics Service, Department of Medicine, Cancer Biology and Genetics Program, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center; Departments of Medicine and Public Health, Weill Cornell Medical College, New York, NY 10065, USA.

Abstract

The cloning of the breast cancer susceptibility genes *BRCA1* and *BRCA2* nearly two decades ago helped set in motion an avalanche of research exploring how genomic information can be optimally applied to identify and clinically care for individuals with a high risk of developing cancer. Genetic testing for mutations in *BRCA1*, *BRCA2*, and other breast cancer susceptibility genes has since proved to be a valuable tool for determining eligibility for enhanced screening and prevention strategies, as well as for identifying patients most likely to benefit from a targeted therapy. Here, we discuss the landscape of inherited mutations and sequence variants in *BRCA1* and *BRCA2*, the complexities of determining disease risk when the pathogenicity of sequence variants is uncertain, and current strategies for clinical management of women who carry *BRCA1/2* mutations.

Up to 15% of patients diagnosed with invasive breast cancer have at least one first-degree female relative (mother, sister, or daughter) with the disease (1). A family history of breast cancer has long been thought to indicate the presence of inherited genetic events that predispose to this disease. Two decades ago, this association was confirmed when extensive studies of families with multiple cases of early-onset (<50 years of age) breast cancer led to the identification of two major breast cancer susceptibility genes, *BRCA1* and *BRCA2* (2–4). More than one million individuals now have been tested for mutations in *BRCA1* and *BRCA2*. Pathogenic mutations appear to account for ~30% of high-risk breast cancer families and explain ~15% of the breast cancer familial relative risk (the ratio of the risk of disease for a relative of an affected individual to that for the general population) (Fig. 1) (5–8).

[*]Corresponding author. couch.fergus@mayo.edu.

Genetic testing for mutations in *BRCA1*, *BRCA2*, and other breast cancer susceptibility genes has served as a model for the integration of genomics into the practice of personalized medicine, with proven efficacy as a tool to determine eligibility for enhanced screening and prevention strategies, as well as a marker for targeted therapy. Here, we discuss the landscape of inherited mutations and sequence variants in *BRCA1* and *BRCA2*, the complexities of determining disease risk when the pathogenicity of sequence variants is uncertain, and current strategies for clinical management of women who carry *BRCA1/2* mutations known to confer a high risk of breast and ovarian cancers. We also extend the discussion to consideration of the current clinical utility of genetic testing for mutations in other predisposition genes and common genetic variants that contribute to breast cancer risk.

Landscape of Mutations in *BRCA1* and *BRCA2* and the Cancer Risk They Confer

More than 1800 distinct rare variants—in the form of intronic changes, missense mutations, and small in-frame insertions and deletions—have been reported in *BRCA1* and 2000 in *BRCA2* (Breast Cancer Information Core; www.research.nhgri.nih.gov/bic). In *BRCA1*, missense mutations that are pathogenic and highly penetrant (i.e., confer a high risk of cancer) are located primarily in the RING finger and BRCT domains (2, 9, 10), which are critical for the DNA repair activity of *BRCA1*. In *BRCA2*, highly penetrant, pathogenic missense mutations are located predominantly in the DNA binding domain (11, 12). Large genomic rearrangements occur in both genes but are more prevalent in *BRCA1* (14% of mutations) than in *BRCA2* (2.6% of mutations) due to the large number of Alu repeats in the genomic region containing the *BRCA1* gene (13). Founder mutations (common mutations in a population arising from a small number of individuals) in *BRCA1* and *BRCA2* have been described in almost every population studied. The best known are in the Ashkenazi Jewish population, with 3% of individuals carrying one of the three founder mutations, namely *BRCA1* c.68_69delAG [185delAG] (1%), *BRCA1* c.5266dupC [5382insC] (0.13%), or *BRCA2* c.5946delT [6174delT] (1.52%) (14, 15). Other examples are the *BRCA1* c.548-?_4185+?del [ex9-12del] mutation found in ~10% of Hispanic *BRCA* carriers and deletions of *BRCA1* seen in Dutch founder populations (16, 17). Thus, targeted screening for specific *BRCA1* and *BRCA2* mutations before full gene testing is warranted in a number of populations.

As studies of *BRCA1* and *BRCA2* unfolded, it became apparent that the estimates of penetrance (risk) of breast and ovarian cancer varied by the ascertainment criteria for studies, with population-based studies showing much lower risks than family-based studies (18). In clinical practice, *BRCA1* mutation carriers are generally estimated to have a 57% chance of developing breast cancer and a 40% chance of developing ovarian cancer by age 70, whereas *BRCA2* mutation carriers are estimated to have a 49% chance of breast cancer and an 18% chance of ovarian cancer (19). Interindividual variability in the risk of breast and ovarian cancer has been attributed to modifying environmental and genetic effects, including the location and type of mutations in *BRCA1* and *BRCA2*. Specifically, early reports focused on the location of mutations in *BRCA1*/*2* suggested that nonsense and frameshift mutations located in the central regions of either coding sequence, termed ovarian

cancer cluster regions (OCCR), were associated with a greater risk of ovarian cancer than similar mutations in the proximal and distal regions of each gene (20–22). More recently, a Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) study of 19,581 *BRCA1* and 11,900 *BRCA2* mutation carriers confirmed relative increases in ovarian cancer and decreases in breast cancer risk for mutations in the central region of each gene and higher risk of breast cancer for mutations in the 5′ and 3′ regions of each gene. Variability in risk is also partly explained by common genetic modifiers of breast and ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers that have been identified through genome-wide association studies (23–29). Accounting for these modifiers suggests that the *BRCA1* mutation carriers in the highest risk category may have an 81% or greater chance of breast cancer and a 63% or greater chance of ovarian cancer by age 80, whereas *BRCA2* mutation carriers at greatest risk may have more than an 83% chance of breast cancer by age 80 (27, 28). In conjunction with other variables modifying risk in *BRCA1* and *BRCA2* mutation carriers, these data offer the potential for more precise personalized risk estimates.

The Challenge of *BRCA1/2* Variants of Uncertain Significance and Variants That Confer Low to Moderate Cancer Risk

As described above, multiple mutations have been identified in *BRCA1/2* that inactivate the corresponding protein and increase the risk of cancer. However, many variants of uncertain significance **(**VUS), including missense, intronic, and small in-frame insertion/deletion variants, also have been observed. Although Myriad Genetics Laboratories has been able to classify many variants as neutral or pathogenic using proprietary data, other clinical testing laboratories offering *BRCA1* and *BRCA2* genetic testing cannot provide interpretation for many of the VUS encountered during testing due to limited information. In an effort to improve the classification process, the Clinvar (www.ncbi.nlm.nih.gov/clinvar) database has been posting results from some of the *BRCA1* and *BRCA2* clinical genetic testing conducted in the United States. Evaluation of VUS has often relied on error-prone models that predict the functional impact of variants on the basis of amino acid conservation and/or structure. However, the development of quantitative risk prediction methods by the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) has substantially improved assessment of the pathogenicity of VUS (30). This method estimates the probability of pathogenicity for each variant using combined evolutionary sequence conservation (Align-GVGD) (31), family-based segregation and cancer history, tumor pathology, and RNA splicing effects (12, 32, 33), and has resulted in classification of many *BRCA1* and *BRCA2* VUS as pathogenic or of neutral/low effect (33). Because this method often lacks statistical power due to the rarity of the individual VUS, quantitative cell-based in vitro assays that evaluate the effect of variants on established functions of the BRCA1 and BRCA2 proteins, with known sensitivity and specificity for pathogenic variants, have been developed for classification of *BRCA1* and *BRCA2* VUS (12, 34–36). Moving forward, interpretation of VUS pathogenicity will likely involve integration of functional, family, and pathology information in predictive models (37).

The classification of VUS may be further complicated by hypomorphic mutations in both *BRCA1* and *BRCA2*, which retain partial protein activity and may be associated with

moderate to low risks of breast and ovarian cancer. The best characterized of these mutations is the p.Arg1699Gln (R1699Q) missense mutation in the BRCT domain of BRCA1 that abrogates the repression of microRNA-155 (38) and is associated with a cumulative risk of breast cancer of 24% by age 70 (30). This risk is lower than that associated with other *BRCA1* mutations but substantially greater than the 12% risk of breast cancer in the general population. In contrast, the well-known polymorphic stop codon in *BRCA2*, p.Lys3326X, is associated with only a modest increase in breast cancer risk [odds ratio (OR) = 1.26] (39) and appears to have little clinical relevance. As more moderate risk variants in *BRCA1* and *BRCA2* are validated, risk management strategies distinct from those applied to carriers of high-risk mutations must be developed.

Clinical Management of Women Carrying Pathogenic *BRCA1/2* Mutations

Several general strategies can be used to reduce cancer risk, morbidity, and mortality in women who carry pathogenic *BRCA1/2* mutations: (i) regular screening by imaging to detect tumors at an early stage; (ii) prophylactic surgeries—risk-reducing mastectomy (RRM) and/or risk-reducing salpingo-oophorectomy (RRSO) (removal of the ovaries and fallopian tubes); and (iii) chemoprevention. In early studies, mammographic screening was found to have limited efficacy in detecting breast tumors in these high-risk women at an early, clinically actionable stage. Fully 29% of de novo tumors were missed by mammography but were found as a palpable mass after a normal screening examination, and a third of these tumors were detected when they had already metastasized to the lymph nodes (40). The limited success of mammography in this setting may result from difficulty in interpreting mammograms in young women with hereditary breast cancers who tend to have a higher breast density than older women, and because these hereditary cancers are often aggressive, rapidly growing “triple-negative” tumors (negative for estrogen and progesterone receptors and lacking HER2/neu amplification) (41). In contrast, magnetic resonance imaging (MRI) detects twice as many breast cancers in *BRCA1/2* mutation carriers as mammography or sonography (40), is associated with rates of interval cancers of less than 10%, and is now considered the standard of care. However, the increased sensitivity also results in increased false-positive rates, with 11% of women undergoing MRI with mammographic screening having biopsies that turned out to be benign, compared with 5% with mammographic screening alone (42–47).

Prophylactic surgical approaches are highly effective, with RRM reducing the risk of breast cancer by at least 90% in *BRCA1/2* mutation carriers (48, 49). However, due to the sensitivity of early detection using MRI, ~64% of women in the United States and 78% in Canada choose to avoid this surgery (50). In contrast, RRSO has become the standard of care for all women who carry highly penetrant *BRCA1/2* mutations because ovarian cancer screening methods using serum markers and imaging are largely ineffective (51, 52). RRSO has been shown to reduce the risk of *BRCA*-associated gynecologic cancer by 80 to 96% (53–55) and to reduce the risk of breast cancer by ~50%, most likely through the induction of premature menopause (54–56). Strikingly, RRSO has been shown to reduce the overall mortality of women by 60% with pathogenic *BRCA1* and *BRCA2* mutations (49). However, a 0.2% annual risk of cancer of the peritoneal lining around the ovaries and fallopian tubes remains because these tissues cannot be surgically removed by RRSO (53). Nonetheless,

genetic testing for *BRCA1/2* mutations and RRSO provided an early example of the deployment of "personalized" prevention through genetics (40, 57).

Another clinical strategy found to reduce cancer risk in women with *BRCA1/2* mutations is hormonal chemoprevention. Antiestrogen therapy has been shown to decrease the risk of primary breast cancer in women at high risk who decided to retain their breast tissue, with several studies demonstrating up to 40 to 50% reduction in the risk of breast cancer in *BRCA1/2* mutation carriers taking antiestrogens such as tamoxifen (58, 59). Oral contraceptives also have been proposed as a strategy to decrease risk of cancer in women with intact ovaries, but with conflicting results. Some studies have shown a decrease in ovarian cancer risk in *BRCA1/2* mutation carriers by up to 60% with 3 or more years of oral contraceptive use (60, 61), whereas other studies have found a 30 and 50% increase in risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers, respectively, with oral contraceptives use for 5 or more years (62, 63).

The identification of mutated genes that predispose to cancer often raises hope that understanding the biology of the corresponding proteins will lead to the development of new "targeted" therapies for patients. Establishing new paradigms in the application of genetics to personalized cancer care, the biology of *BRCA1* and *BRCA2* mutant tumors appears to be particularly well suited to specific therapies. In vitro and in vivo experiments and clinical trials have shown that platinum chemotherapy is effective against *BRCA1* (and, by analogy, *BRCA2*) mutant tumors, in part because platinum generates interstrand cross-links that can only be adequately repaired by *BRCA1*- and *BRCA2*-dependent homologous recombination (HR) DNA repair (64). Mutations in *BRCA1/2* also sensitize cells to the inhibition of poly(ADP-ribose) polymerase (PARP), an enzyme involved in base excision repair (65, 66). Pharmacologic inhibition of PARP enzymatic activity in the background of *BRCA*-associated defects in HR-mediated DNA repair results in chromosomal instability, cell cycle arrest, and apoptosis. However, the exact mechanisms by which PARP inhibitors (PARPi) disrupt tumor growth remain to be fully delineated (67). Clinical trials have explored the efficacy of PARPi in the treatment of *BRCA1* and *BRCA2* mutant breast, ovarian, pancreatic, prostate, and other cancers, and it is likely that at least one of the four compounds entering phase II clinical trials this year will be licensed for widespread use (68). However, not all *BRCA* mutation carriers respond to these agents alone or in combination with chemotherapy. Indeed, studies with mice have suggested that mutations in the N-terminal BARD1 binding domain of *BRCA1*, such as the relatively common p.Cys61Gly (C61G), may not confer hypersensitivity to PARPi (69). In addition, as is the case with most targeted therapies, tumors can become resistant to these drugs (70, 71). Acquired resistance to PARPi has been associated with multiple mechanisms, including drug metabolism and efflux, post-transcriptional alterations of *BRCA1* or *BRCA2*, secondary mutations that restore the HR activity of *BRCA1* or *BRCA2*, and accumulation of somatic genetic alterations that counteract the sensitivity associated with *BRCA1* or *BRCA2* mutations (72). Whether combination therapies can overcome these complications remains to be determined.

Other Genes that Confer a Moderate to High Risk of Breast Cancer

Several rare cancer-susceptibility syndromes are known to confer a high risk of breast cancer, including Li-Fraumeni syndrome (caused by germline mutations in *TP53)*, Cowden disease (caused by germline mutations in *PTEN*), and Peutz-Jeghers syndrome (caused by germline mutations in *STK11*) (Fig. 1) (73–75). Testing for mutations in these and other genes is part of the clinical management of women with a personal or family history suggestive of these diagnoses. With the advent of massively parallel sequencing and the ongoing delineation of an increasing number of genes mutated in familial breast cancer (for example, *PALB2*) (76), simultaneous screening of large panels of "predisposition" genes is now widely available. These panels have proven effective in identifying individuals and family members at elevated risk of breast and other cancers. However, clinical interpretation of results from the panels is complicated by several factors. In particular, breast cancer penetrance and risk of other cancers has not yet been established for pathogenic mutations in most of the panel genes, and guidelines for clinical management of individuals found to carry these mutations have not been developed (77). Additionally, as is true for *BRCA1/2*, there is a high rate of VUS in the panel genes, the interpretation of which causes anxiety for both the patient and the physician. Furthermore, several commercial panels contain genes such as *APC* and *VHL*, which have not been clearly associated with susceptibility to breast cancer (78). Although continued clinical research is needed to responsibly integrate panel testing to practice, such approaches may provide guidance for critical clinical decisions such as whether a patient is at high risk of contralateral breast cancer and/or should undergo risk reduction surgeries. Conceivably, panel testing also may prove useful for selecting patients for treatment with PARP inhibitors, because several of the genes in current panels encode proteins involved in double-strand break repair, which may influence responsiveness to platinum and potentially PARPi (79).

Polygenic Risk Modeling

Genome-wide association studies (GWAS) of large numbers of breast cancer patients from the general population along with healthy controls have identified common genetic variants in 76 loci associated with small increases in the risk of breast cancer (Fig. 1) (39, 80). The greatest influence on overall breast cancer risk identified through GWAS is associated with the rs35054928 variant in the *Fibroblast Growth Factor Receptor 2* gene (*FGFR2*) (OR = 1.27) (81). However, many of the other variants have minor effects on risk (OR < 1.10) (39). The majority of the known variants are associated with estrogen receptor (ER)–positive breast cancer, but seven loci are specific to ER-negative disease (82). Little is known about the relevance of these risk factors to the different molecular subtypes of breast cancer, although three of these loci (*MDM4*, 19p13.1, and *TERT-CLPTM1L* rs10069690) are exclusive to triple-negative breast cancer (82–85) and *BRCA1*-associated breast cancer (27). Several of the common breast cancer risk variants are associated with established cancer genes such as *BRCA2*, *TGFBR2*, *MYC*, and *TET2* (39), but the underlying biological mechanisms by which most of these common variants influence breast cancer risk are not well understood. Recent evidence suggests that many of these risk loci contain multiple independent risk-associated variants that may have combined effects on gene transcription. For instance, two variants in the 11q31.1 locus with independent effects on breast cancer

risk regulate Cyclin D1 expression by modifying a transcriptional enhancer and a silencer of the *CCND1* gene (86). Similarly, two independent risk-associated single-nucleotide polymorphisms (SNPs) in the *FGFR2* locus induce FOXA1, ERα, and E2F1 binding to enhancers and promote FGFR2 expression (81). Extensive fine-mapping and functional studies are needed to determine how common genetic variants increase breast cancer risk in the general population.

Documentation of the clinical utility of risk-associated SNPs constitutes a key hurdle in the emerging paradigm of polygenic risk assessment for human cancer (84–86). The first such effort for breast cancer showed that 10 breast cancer–associated SNPs, when combined with traditional breast cancer risk markers, had a modest impact on risk prediction models (87). A subsequent study indicated that 15 SNPs added little to discriminatory accuracy but did reclassify 8% to 32% of women for MRI eligibility and 11% to 19% for tamoxifen use (88). In addition, a polygenic risk score (PRS), including 22 SNPs, calculated as the sum of the ORs for each allele, correlated with risk of early onset breast cancer (OR = 3.37, $P = 0.03$) (88). Several studies examining the influence of all known breast cancer–associated SNPs on risk are now under way (85). Overall, it now appears likely that combinations of risk variants will improve stratification of the risk for breast cancer, leading to better identification of women who will benefit from enhanced screening and intervention (89).

Conclusions

The clinical management of breast cancer is continually evolving to incorporate new information emerging from studies of the basic biology of the disease. History provides many examples: the progression of surgical approaches from the Halstead radical mastectomy to sentinel node sampling, the incorporation of gene expression microarrays to subclassify the disease and serve as prognostic biomarkers, and the early development of a targeted therapy (Herceptin) for breast cancers over-expressing the HER2/neu receptor. The role of PARP inhibitors for treatment of breast cancers with *BRCA* mutations has established a new paradigm of targeted therapeutics directed toward an inherited genetic susceptibility. Similarly, the elucidation of the drivers of hereditary breast cancer, characterized by gene-gene and gene-environment interactions of rare mutations and common variants, exemplifies an emerging model of the polygenic basis of this common human malignancy (5–7, 57, 80, 90). As part of personalizing risk assessment, these genomic insights may soon form a rational and cost-effective basis for selection of women for breast cancer screening (91, 92). Going forward, the reduced cost and increased access to genomic profiling of breast tumors will likely identify new therapeutic targets. However, the anticipated increased uptake of sequencing will require new approaches for communication to patients of findings from germline DNA that suggest increased risk for treatment toxicities or risk for disorders other than breast cancer (90, 93, 94). Two decades after the cloning of the *BRCA* genes, clinical application of findings of breast cancer genetic research continues to drive new paradigms of “personalized” genomics and precision medicine.

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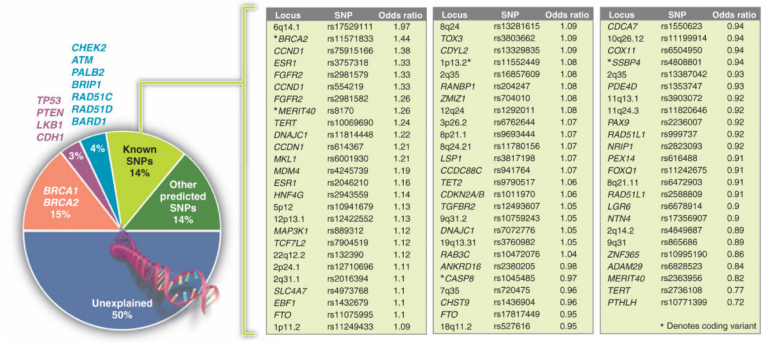

Locus	SNP	Odds ratio
6q14.1	rs17529111	1.97
*BRCA2	rs11571833	1.44
CCND1	rs75915166	1.38
ESR1	rs3757318	1.33
FGFR2	rs2981579	1.33
CCND1	rs554219	1.33
FGFR2	rs2981582	1.26
*MERIT40	rs8170	1.26
TERT	rs10069690	1.24
DNAJC1	rs11814448	1.22
CCDN1	rs614367	1.21
MKL1	rs6001930	1.21
MDM4	rs4245739	1.19
ESR1	rs2046210	1.16
HNF4G	rs2943559	1.14
5p12	rs10941679	1.13
12p13.1	rs12422552	1.13
MAP3K1	rs889312	1.12
TCF7L2	rs7904519	1.12
22q12.2	rs132390	1.12
2p24.1	rs12710696	1.11
2q31.1	rs2016394	1.1
SLC4A7	rs4973768	1.1
EBF1	rs1432679	1.1
FTO	rs11075995	1.1
1p11.2	rs11249433	1.09

Locus	SNP	Odds ratio
8q24	rs13281615	1.09
TOX3	rs3803662	1.09
CDYL2	rs13329835	1.09
1p13.2*	rs11552449	1.08
2q35	rs16857609	1.08
RANBP1	rs204247	1.08
ZMIZ1	rs704010	1.08
12q24	rs1292011	1.08
3p26.2	rs6762644	1.07
8p21.1	rs9693444	1.07
8q24.21	rs11780156	1.07
LSP1	rs3817198	1.07
CCDC88C	rs941764	1.07
TET2	rs9790517	1.06
CDKN2A/B	rs1011970	1.06
TGFBR2	rs12493607	1.05
9q31.2	rs10759243	1.05
DNAJC1	rs7072776	1.05
19q13.31	rs3760982	1.05
RAB3C	rs10472076	1.04
ANKRD16	rs2380205	0.98
*CASP8	rs1045485	0.97
7q35	rs720475	0.96
CHST9	rs1436904	0.96
FTO	rs17817449	0.95
18q11.2	rs527616	0.95

Locus	SNP	Odds ratio
CDCA7	rs1550623	0.94
10q26.12	rs11199914	0.94
CCNY1	rs6504950	0.94
*SSBP4	rs4808801	0.94
2q35	rs13387042	0.93
PDE4D	rs1353747	0.93
11q13.1	rs3903072	0.92
11q24.3	rs11820646	0.92
PAX9	rs2236007	0.92
RAD51L1	rs999737	0.92
NRIP1	rs2823093	0.92
PEX14	rs616488	0.91
FOXQ1	rs11242675	0.91
8q21.11	rs6472903	0.91
RAD51L1	rs2588809	0.91
LGR6	rs6678914	0.9
NTN4	rs17356907	0.9
2q14.2	rs4849887	0.89
9q31	rs865686	0.89
ZNF365	rs10995190	0.86
ADAM29	rs6828523	0.84
MERIT40	rs2363956	0.82
TERT	rs2736108	0.77
PTHLH	rs10771399	0.72

* Denotes coding variant

Fig. 1. Genetic variants that predispose to breast cancer

The pie chart on the left shows the estimated percentage contribution of mutations in highpenetrance (*BRCA1/2*, *TP53*, *CDH1*, *LKB1*, and *PTEN*) and moderate-penetrance (e.g., *CHEK2*, *ATM*, and *PALB2*) genes and common low-penetrance genetic variants to familial relative risk. Common genetic variants are denoted as SNPs. “Known SNPs” are SNPs associated with breast cancer through GWAS, as listed on the right. The odds ratios refer to the increase (or, in some cases, the reduction) in risk conferred by the rare allele of the variants. “Other predicted SNPs” refers to the estimated contribution of all SNPs, other than known loci, that were selected for replication of breast cancer GWAS (5, 39).