The biological effects and clinical implications of BRCA mutations: where do we go from here?

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BRCA1 and BRCA2 are tumour-suppressor genes encoding proteins that are essential for the repair of DNA double-strand breaks by homologous recombination (HR). Cells that lack either BRCA1 or BRCA2 repair these lesions by alternative, more error-prone mechanisms. Individuals carrying germline pathogenic mutations in BRCA1 or BRCA2 are at highly elevated risk of developing breast and/or ovarian cancer. Genetic testing for germline pathogenic mutations in BRCA1 and BRCA2 has proved to be a valuable tool for determining eligibility for cancer screening and prevention programmes. In view of increasing evidence that the HR DNA repair pathway can also be disrupted by sequence variants in other genes, screening for other BRCA-like defects has potential implications for patient care. Additionally, there is a growing argument for directly testing tumours for pathogenic mutations in BRCA1, BRCA2 and other genes involved in HR-DNA repair as inactivation of these genes may be strictly somatic. Tumours in which HR-DNA repair is altered are most likely to respond to emerging targeted therapies, such as inhibitors of poly-ADP ribose polymerase. This review highlights the biological role of pathogenic BRCA mutations and other associated defects in DNA damage repair mechanisms in breast and ovarian cancer, with particular focus on implications for patient management strategies.

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INTRODUCTION

BRCA1 and BRCA2 are tumour-suppressor genes located on chromosomes 17q21 and 13q12, respectively.1-4 Functional BRCA proteins are involved in the maintenance of genome stability through repair of DNA double-strand breaks (DSBs) by homologous recombination (HR), cell growth regulation and control of cell division.5,6 Individuals carrying monoallelic germline pathogenic mutations in BRCA1 or BRCA2 (BRCA1/2) are at higher risk of developing a variety of cancers, particularly breast and/or ovarian cancer. Meta-analyses have indicated a mean cumulative breast cancer risk at age 70 years to be 57% (95% CI 47–66%) for patients carrying the BRCA1 pathogenic mutations and 49% (95% CI 40–57%) for patients carrying the BRCA2 pathogenic mutations.7 The equivalent mean cumulative ovarian cancer risk is 40% (95% CI 35–46%) for patients carrying the BRCA1 pathogenic mutations and 18% (95% CI 13–23%) for patients carrying the BRCA2 pathogenic mutations.7 A prospective epidemiological study (EMBRACE) showed that carriers of BRCA1 and BRCA2 pathogenic mutations have a mean cumulative risk of breast cancer at age 70 years of 60% (95% CI 44–75%) and 55% (95% CI 41–70%), respectively.8 The equivalent mean cumulative ovarian cancer risk is 59% (95% CI 43–76%) and 16.5% (95% CI 7.5–34%), respectively.8 Tumourigenesis in germline BRCA1/2 pathogenic mutation carriers generally follows a two-hit hypothesis, the first ‘hit’ owing to the inherited pathogenic mutation of one BRCA allele and the second ‘hit’ owing to the somatic inactivation of the second-wild-type allele.9-11 Increasing evidence suggests that other types of breast and ovarian cancers share genomic and phenotypic similarities with tumours associated with germline and somatic BRCA1/2 pathogenic mutations.12 Such cases may be sensitive to the same emerging targeted therapies as tumours associated with germline BRCA1/2 pathogenic mutations.

Methods for the detection of BRCA1 and BRCA2 pathogenic mutations are now widely accessible. Until now, the principal aim of BRCA1/2 pathogenic mutation testing has been to enable risk assessment to permit early diagnosis and cancer prevention. However, it is increasingly apparent that knowledge of BRCA status has prognostic utility that can affect treatment decisions and may improve survival.13-15 This review highlights the biological role of BRCA1/2 pathogenic mutations and other associated defects in DNA damage repair in breast and ovarian cancer, with particular focus on implications for clinical management strategies.

BRCA AND REPAIR OF DNA DSBS BY HR

DNA repair is essential for the survival of both normal and cancer cells. DNA repair mechanisms also allow cancer cells to survive the DNA injury imposed by chemotherapy or radiation. An elaborate network of genome surveillance systems and DNA repair mechanisms exist to repair DNA lesions and ensure the integrity of the genome and hence cell fitness and viability. DNA DSBs, in which both strands of the double helix are severed, are the most dangerous type of DNA lesion; if left unrepaired, or repaired incorrectly, DSBs may result in massive loss of genetic information, genomic rearrangements or cell death. Two different mechanisms exist for the repair of DSBs: non-homologous end joining (NHEJ) and HR.16 These pathways differ in their fidelity and template requirements. NHEJ is an intrinsically error-prone pathway, which modifies the broken DNA ends, and ligates them together with little or no homology, generating small deletions or insertions. In contrast, HR is a highly conserved pathway that provides accurate repair of DSBs in the late S and G2 phases of the
cell cycle using the intact sister chromatid as a template to repair the break and maintain sequence integrity.

**BRCA1** and **BRCA2** are key components of the HR pathway, and cells that lack these proteins are unable to repair DSBs by HR.5,9 **BRCA1** appears to have an early and broad role in the promotion and regulation of HR.5,9,17,18 **BRCA1** has been shown to colocalise at sites of DNA damage with RAD51, another key protein involved in HR, while **BRCA1/-deficient** cell lines lack RAD51 foci.19 **BRCA1** appears to regulate HR, at least in part, through a modulatory role in the PALB2-BRCA2-BRCA2 cell lines derived from some patients with Fanconi’s anaemia, also being referred to as **BRCA2**-dependent loading of HR.5,9,17,18

A central role for **BRCA2** in HR was first suggested by evidence showing the acquired chromosomal abnormalities of **BRCA2**-deficient cell lines to be similar to those seen in Fanconi’s anaemia.10,20,21 Furthermore, cell lines derived from some patients with Fanconi’s anaemia were shown to carry biallelic pathogenic mutations in **BRCA2**, which led to **BRCA2** also being referred to as **FANC**D1.20,22 **BRCA2** knockout cells sustain spontaneous aberrations in chromosome structure that accumulate during division in culture.21 In the absence of DNA damage, RAD51 is sequestered by **BRCA2**, prohibiting RAD51 nucleation onto double-stranded DNA (Figure 1). Following DNA damage, **BRCA2** relocates to the site of DNA damage and enables RAD51 nucleation onto single-stranded DNA.23,24

**OTHER CAUSES OF DEFECTS IN HR**

Pathogenic mutations in several other genes involved in HR-mediated DNA repair have been shown to be associated with breast and ovarian cancer predisposition (Figures 2 and 3).25,26 In the Cancer Genome Atlas Research Network analysis of high-grade serous ovarian adenocarcinomas, genomic alterations in 26% of HR genes other than **BRCA1/2** were observed, including amplification or pathogenic mutation of **EMSY** (8%), promoter methylation of **RAD51C** (3%), pathogenic mutation of **ATM/ATR** (2%) and pathogenic mutation of Fanconi’s anaemia genes (5%) (Figure 2).25 In addition, focal deletion or pathogenic mutation of **PTEN** (7%) has been observed; however, the role of **PTEN** in HR or as a surrogate of HR deficiency remains to be determined. Such cancers are said to display ‘**BRCA1eness**’ if they exhibit similar DNA repair defects to those seen in **BRCA1/-deficient** cells.27

Monoallelic germline pathogenic mutations in **PALB2**, **BRIP1** and **ATM** have been shown to be associated with an increased breast cancer relative risk of approximately 2–3.28–32 Biallelic pathogenic mutations in **PALB2** and **BRIP1** have been observed in patients with Fanconi’s anaemia, resulting in their alternative names of **FANCN** and **FANCJ**, respectively.33,34 More recently, **BRIP1** pathogenic mutations have also been demonstrated in patients with ovarian cancer.35 The frequency of germline **PALB2** pathogenic mutations in ovarian cancer cases does not appear increased as compared with the general population.36 **PALB2** encodes the partner and localiser of **BRCA2** protein, which stabilises the **BRCA2** protein and anchors it to structures within the nucleus, allowing the **BRCA2** protein to mediate DNA repair.26 **BRIP1** – also known as **BACH1** – encodes **BRCA1**-interacting protein-terminal helicase 1, a DNA helicase that influences the DNA repair ability and tumour-suppressor function of **BRCA1**.37 **ATM** is a protein kinase with a key role in sensing DNA DSBs and monitoring their repair. Biallelic germline inactivation of **ATM** is responsible for the neurodegenerative disorder ataxia-telangiectasia.38

The RAD51 paralogues, RAD51C and RAD51D, also have an integral role in the repair of DNA DSBs through HR.39 To date, germline pathogenic mutations in **RAD51** have not been observed in patients with breast or ovarian cancer, suggesting that they are lethal. However, **RAD51C** pathogenic mutations have been identified in up to 2.9% of highly penetrant breast and ovarian cancer families who previously screened negative for **BRCA1/2** pathogenic mutations.40–42 Ovarian cancer occurrence in families with **RAD51C** pathogenic mutations shows major similarities with families carrying **BRCA1/2** pathogenic mutations. In addition, as these families show apparent segregation of the pathogenic mutation with the cancer phenotype, the penetrance of **RAD51C** pathogenic mutations is predicted to be comparable to that of **BRCA2** pathogenic mutations (Antoniou, unpublished data). However, the mean age at onset for ovarian cancer observed in women with **RAD51C** pathogenic mutations is approximately 60 years, which is older than in **BRCA1** pathogenic mutation carriers (51 years).43 The paralogues **RAD51B**, **RAD51D** and **XRCC2** are also associated with an increased ovarian

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**Figure 1** Role of **BRCA2** in DNA DSB repair by HR. Diagram courtesy of Gaël Millot, Curie Institute and University Pierre and Marie Curie, Paris, France.23,24
PARP function results in the repair of certain kinds of DNA damage, particularly in the absence of HR. Loss of PARP function leads to synthetic lethality with the HR pathway, in which poly-ADP ribose polymerase (PARP) has a major role, important for the repair of certain kinds of DNA damage, particularly in the absence of HR. Loss of PARP function results in the accumulation of single-strand DNA breaks, which are subsequently converted to DSBs by cellular transcription and replication. These DSBs, which are typically repaired by HR or NHEJ in normal cells, would accumulate in HR-deficient cells, leading to subsequent cell death.

Loss of PARP1 function induces the formation of nuclear RAD51 foci as a result of the increased formation of DNA lesions that need to be repaired by the HR pathway. Two pivotal preclinical studies demonstrated loss of these RAD51 foci in BRCA1- and BRCA2-deficient cells after PARP inhibitor exposure. Sensitivity to PARP inhibition has also been observed in cells with defects in HR other than BRCA deficiency. Several PARP inhibitors are now in various stages of clinical development.

Olaparib is a potent oral PARP inhibitor that has been shown to induce synthetic lethality in BRCA1/2-deficient tumour cells. Anti-tumour activity of olaparib has been demonstrated in patients with BRCA-mutated breast and ovarian cancer in proof-of-concept trials. In a Phase II trial, maintenance therapy with olaparib was shown to significantly prolong progression-free survival in patients with platinum-sensitive relapsed serous ovarian cancer compared with placebo, with the greatest benefit seen in patients with a pathogenic BRCA mutation. An 82% reduction in risk of disease progression with olaparib compared with placebo was seen in patients with pathogenic BRCA mutations. Further studies of olaparib and other PARP inhibitors in this setting are ongoing.

In addition to potential utility for the treatment of tumours harbouring a pathogenic BRCA1/2 mutation, PARP inhibition might also be a useful therapeutic approach for the treatment of a wider range of tumours bearing a variety of deficiencies in the HR pathway and thus displaying properties of ‘BRCAness’. Methods to identify patients most likely to benefit from these emerging therapies are therefore required.
family history, young age at onset, male breast cancer and multiple
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In unselected breast cancer, the reported pathogenic BRCA mutation
certainty is lower at 1–5%, whereas in unselected ovarian cancer the reported
frequency is higher at 6–16%. It should be noted that these
ranges exclude studies in male breast cancer and Ashkenazi Jewish
women. Higher prevalence is associated with factors such as a positive
family history, young age at onset, male breast cancer and multiple
tumours in the same patient or certain histological characteristics.

In an Australian population-based, case–control study, 1001 women
with newly diagnosed histologically confirmed, non-mucinous,
invasive epithelial ovarian, peritoneal or fallopian tube cancer were
screened for point mutations and large rearrangements in BRCA1 and
BRCA2. Pathogenic BRCA1/2 mutations were identified in 14.1% of
patients (141 mutations in 1001 women; 95% confidence interval 11.9,
16.3). Of these 141 pathogenic mutations, 88 were in BRCA1 (62.4%)
and 53 were in BRCA2 (37.6%). BRCA1/2 pathogenic mutations
were seen in 16.6% of serous tumours, 16.8% of high-grade tumours
and 17.1% of all high-grade serous tumours. Of note, 44% of women
with BRCA1/2 germline pathogenic mutations in this study had no
previous family risk factors.

In a study of 489 high-grade serous ovarian adenocarcinomas,
64/316 (20.3%) tumours with sequenced exomes (n = 316) were found
to harbour pathogenic BRCA1 or BRCA2 mutations; two tumours
were observed to harbour both BRCA1 and BRCA2 mutations.

The majority of detected BRCA1/2 pathogenic mutations were germline
in origin (71%), corresponding to a germline pathogenic variant
frequency of 14.6% and a somatic pathogenic variant frequency of
6.0%. Accompanying heterozygous loss was observed with 81 and 72%
of BRCA1 and BRCA2 pathogenic mutations, respectively, indicating
inactivation of both alleles, as predicted by Knudson’s two-hit
hypothesis for a tumour-suppressor gene. In addition to BRCA1/2
pathogenic mutations, 34/316 (10.8%) of tumours had lost BRCA1
expression through BRCA1 promoter methylation. Epigenetic silencing
of BRCA1 was shown to be mutually exclusive of germline
BRCA1/2 pathogenic mutations (Figure 2). Survival analysis based on
BRCA status revealed divergent outcomes, with longer overall survival
for BRCA-mutated cases compared with BRCA wild-type and BRCA1
epigenetically silenced cases, respectively (Figure 2). These data
would suggest that a broader range of patients with ovarian cancer
should now be tested, perhaps offering BRCA testing to all but patients
whose tumours have mucinous histology.

So far, the low frequency of heterozygotes for BRCA pathogenic
mutations relative to the high incidence of breast and ovarian cancer,
coupled with the high costs of BRCA testing, has rendered exhaustive
testing of all patients with breast and ovarian cancer impractical.
However, the evolution of multiple gene panel sequencing and the
decreasing cost of genetic testing are allowing health-care budgets to
offer pathogenic BRCA mutation testing to broader populations without
a significant impact on cost.

**PATHOGENIC BRCA MUTATION TESTING FOR CANCER PREVENTION**

The estimated population frequency of pathogenic BRCA1/2 mutations
is 1:800–1:1000 per gene; however, the prevalence of BRCA1/2
germline pathogenic mutations varies considerably between different
ethnic groups and geographical areas. BRCA1 and BRCA2 pathogenic
mutation frequency in patients with breast and ovarian cancer
unselected for family history or age at onset is generally low.

At present, the selection of appropriate candidates for testing is typically
based on country-specific guidelines or by larger international societies.

Widely accepted clinical criteria for referral include family history and
age at cancer onset. Based on these criteria, pathogenic mutations in
BRCA1 or BRCA2 are typically identified in 12–15% of tested cases.

Guidelines in some countries require a 10–20% probability of
detecting a BRCA1/2 pathogenic mutation within a family before
mutational analysis is considered. A number of predictive models and
scoring systems have been developed to assess the probability of
a pathogenic BRCA1/2 mutation in a given individual dependent
on their family history, with varying degrees of validation. These include
BRCAPRO, BOADICEA or the Manchester Scoring System.
that compute carriage probabilities are the most predictive but require specific computer software and data entry for all family members can be time-consuming. Scoring systems avoid data entry, are a good proxy to probability computations and can generally be easily modified to include new relevant predictive factors.76 The Manchester scoring system allocates a score to each affected individual in a family and computes the sum of the scores in the maternal and paternal lineage to determine whether or not a genetic test is recommended.77,78 The Manchester scoring system is empirical as the scores have been determined to fit the observations made in a group of selected families tested for pathogenic BRCA1/2 mutations. It does not take into account information on unaffected family members, the presence of which is expected to decrease the probability of mutations, and gives the same weight to all affected family members whatever their degree of kinship.

An alternative system has been recently developed, which has been shown to be superior to the Manchester scoring system.76 The new scoring system is based on the conditional probability P that a proband is a carrier, given all relevant predictive information in the family. Parameters taken into account include pathogenic BRCA1/2 mutation frequencies in the population, as well as breast and ovarian cancer risks in carriers and non-carriers. The performance of the new scoring system was evaluated using a simulation of 10 million families, built from women affected with breast or ovarian cancer at different ages.76,79 At a score threshold of 5, where positive predicted value (PPV) (15%; ie, percentage of carriers among tested individuals) and specificity (87%; ie, percentage of non-tested individuals among non-carriers) are similar to the Manchester scoring system with a pathogenic mutation probability of 10%, sensitivity (ie, percentage of tested individuals among carriers) with the new scoring system was higher than the Manchester scoring system (77 vs 72%).76 The improved performance of the new scoring system compared with the Manchester scoring system was attributed to accounting for unaffected family members and for the degree of kinship of relatives with the proband.

**PATHOGENIC BRCA MUTATION TESTING FOR CANCER TREATMENT**

Pathogenic BRCA mutation testing on a broader population is likely to result in increased numbers of relatives screened, which may subsequently reduce the future incidence of ovarian cancer, as those relatives who are shown to harbour a pathogenic BRCA mutation can be started on a cancer prevention programme. Despite mutation detection threshold (PPV) lowering,76 there remains a need to broaden BRCA1/2 testing criteria in order to optimise use of BRCA testing to guide treatment decisions. One approach to broadening BRCA1/2 testing criteria is by introducing individual criteria, such as including women with triple-negative (TN) breast cancer (ie, negative for oestrogen receptor, progesterone receptor expression and HER2 amplification) and women with high-grade ovarian cystoadenocarcinoma.

In one recent analysis,79 probabilities for the TN status of a breast tumour were obtained from the proportion of TN tumours among women tested for BRCA1/2 in studies without any selection on morphological characteristics.80–83 A Bayesian model was developed to calculate the probability of a pathogenic BRCA1 mutation according to age at diagnosis, assuming the rate of TN disease to be 68% among women with a pathogenic BRCA1 mutation and 13% among women with no pathogenic BRCA1 mutation (including those with a pathogenic BRCA2 mutation). Results showed the probability of a pathogenic BRCA1 mutation to be high at 23% in women diagnosed with TN breast cancer at < 35 years, compared with 9.2% in women diagnosed at 35–39 years, 5.5% at 40–49 years, 4.3% at 50–59 years and 2.5% at 60–69 years (unpublished data). Thus TN disease status appears to be a good marker for pathogenic BRCA1 mutations especially in young women with breast cancer.

Including individual criteria – specifically, ovarian cancer before age 61 years (except borderline, mucinous tumours), breast cancer before age 36 years, TN breast cancer before age 51 years and male breast cancer at any age – into one predictive model increased sensitivity to 77% (a gain of 13% compared with use of French family criteria alone), with slight reductions in PPV (11%) and specificity (82%).76,79 However, the ‘cost’ of introduction of individual criteria was to increase the number of tests by 49%.

In order to maximise the potential of emerging therapies, such as PARP inhibitors and agents targeting other proteins involved in DNA repair mechanisms, identification of patients with germline pathogenic mutations in other genes or biallelic somatic inactivation of genes involved in DNA repair is likely to become increasingly important. There is increasing interest in confirming the pathogenicity of many sequence variants in the BRCA1/2 genes whose pathogenicity is currently unknown, as well as other genes in the HR-pathway. Three groups have recently reported similar genomic ‘scars’, which appear to be potential surrogate markers of HR deficiency and potential sensitivity to DNA-damaging agents. These include a HR deficiency score based on genome-wide loss of heterozygosity,84 a telomeric allelic imbalance score85 or large-scale genomic instability.86 The potential clinical application of genomic ‘scars’ include facilitating the use of PARP inhibitors and platinum-based chemotherapy in breast, ovarian and other cancers;84 identifying cancer patients likely to benefit from treatments targeting defective DNA repair;85 and easing the challenge of selecting patients for genetic testing or recruitment to clinical trials of novel emerging therapies that target DNA repair deficiencies in cancer.86 Such genomic ‘scars’ would appear to merit further study as potential biomarkers of response to emerging targeted therapies; however, direct testing of BRCA/HR-associated genes by Next-Generation Sequencing (NGS) without investigating for such markers may be more practical.

The evolution of genetic testing may allow a more accessible option for broader testing strategies. NGS is an efficient and cheaper alternative to sequential testing, allowing simultaneous screening of multiple cancer susceptibility genes. Assessing multiple gene panels will allow individualised testing dependent upon the risk for the individual from factors such as age, ethnicity or likelihood of inherited predisposition by family history of disease.87 In the future, it is anticipated that more panels of genes linked to HR defects and cancer risks will be available at a lower cost.87 In addition, the use of such gene panels directly on tumours in order to identify biallelic somatic events is an important issue and a technological challenge. It is of course important, whatever the strategy used, that patients are kept well informed of the testing process.

**CONCLUSIONS**

It is increasingly apparent that the HR pathway for DNA repair is not only disrupted by germline and somatic pathogenic BRCA1/2 mutations but also by pathogenic mutations in other genes involved in HR. The presence of BRCA-like defects in patients with breast and ovarian cancer can be used to inform clinical management decisions. As such, there is a clear need to broaden the criteria for BRCA1/2 germline genetic testing, as well as to expand testing to include identification of germline pathogenic mutations in other genes that may be involved in DNA damage repair by HR DSBR. Furthermore, tumour markers of ‘BRCaness’ may have utility for the identification of patients most...
likely to respond to emerging targeted therapies, such as PARP inhibitors. With the rapid evolution of multi-panel genetic sequencing, coupled with the decreasing cost of genetic testing, BRCA testing and individualised screening is becoming more accessible.

CONFICT OF INTEREST

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