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Can genetic testing guide treatment in breast cancer?

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ABSTRACT

In the last 15 years, our understanding of genes that predispose to breast cancer has increased enormously. Germline alleles have been identified that have a modest effect on the risk of breast cancer, but there remain only a handful of genes in which mutation substantially elevates the risk of breast cancer. These include *BRCA1*, *BRCA2*, *TP53* and *PTEN*. Whilst breast cancer occurring in patients in Li-Fraumeni and Cowden's syndrome families is of great importance, the more frequent scenario is that of women, or indeed of men, presenting with breast cancer with an underlying germline mutation in *BRCA1* or *BRCA2*. Should these individuals be treated differently because they have had a breast cancer or are at risk of the disease because of a *BRCA1* or *BRCA2* mutation?

In this review, we consider whether *BRCA1* or *BRCA2* mutation influences the choice of breast screening and breast cancer prevention strategies. Furthermore, for women with an established breast cancer whether their mutation directly influences (1) baseline prognosis, (2) the results of local surgical and radiation therapy, (3) the benefits from adjuvant systemic therapy and finally (4) whether selection or avoidance of particular systemic agents is guided by the presence of a *BRCA1* or *BRCA2* germline mutation?

1. Introduction

In the last 15 years, our understanding of genes that predispose to breast cancer has increased enormously. More recently, a number of germline alleles have been identified that have a modest effect on the risk of breast cancer,[1] but there remain only a handful of genes in which mutation substantially elevates the risk of breast cancer. These include *BRCA1*, *BRCA2*, *TP53* and *PTEN*.[2] Whilst breast cancer occurring in patients in Li-Fraumeni and Cowden's syndrome families is of great importance, the more frequent scenario is that of women, or indeed of men, presenting with breast cancer with an underlying germline mutation in *BRCA1* or *BRCA2*. The question that these patients and their doctors want to know is whether they should be treated differently because they have had a breast cancer or are at risk of the disease because of a *BRCA1* or *BRCA2* mutation?

To answer this question we need to consider whether *BRCA1* or *BRCA2* mutation influences the choice of breast screening and breast cancer prevention strategies. Furthermore, for women with an established breast cancer whether their mutation directly influences (1) baseline prognosis, (2) the results of local surgical and radiation therapy, (3) the benefits from adjuvant systemic therapy and finally (4) whether selection or avoidance of particular systemic agents is guided by the presence of a *BRCA1* or *BRCA2* germline mutation?

2. The biology of BRCA1 and BRCA2

Increasingly, comprehensive information is becoming available on the functions and biology of BRCA1 and BRCA2 proteins, which can inform these issues (reviewed in *Oncogene* (2006) special issue 25). Although similarly named BRCA1

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and BRCA2 are very different in terms of structure and in several of their cellular roles. Whilst BRCA1 functions in processes as diverse as chromatin modelling, transcriptional regulation, DNA decatenation and the DNA damage response,[3] the established predominant functions of BRCA2 relate to the maintenance of genome stability through DNA repair by homologous recombination and the regulation of cell separation after division.[4] Despite the controversies about BRCA1 and BRCA2 haploinsufficiency, there are several lines of evidence to suggest that there is no functional consequence until both *BRCA1* and *BRCA2* alleles are lost, mutated or silenced.[5,6] This is consistently observed in malignant tissue in *BRCA1* or *BRCA2* mutation carriers.[7–9] It is the loss of faithful DNA repair and genome stability functions in the pre-malignant tissues that drive the rapid acquisition of mutation as is evidenced by the profound chromosomal instability of *BRCA1* or *BRCA2* mutation-associated breast and ovarian cancers. In contrast, the normal tissues of a carrier are heterozygous for the mutation, and retain a wild-type allele and ostensibly normal gene function. It is this tumour tissue specific functional deficiency that may afford opportunity for genotype-based tumour selective targeted therapies as will be discussed later in this review.

2.1. *What are the defining features of BRCA1 and BRCA2 mutation-associated breast cancers?*

Breast cancers associated with mutations in either *BRCA1* or *BRCA2* tend to be of high histological grade, show a high frequency of mitoses, frequently lose p53 function and rarely amplify the *HER2* oncogene but this is where similarity ceases.[10] A consistent theme emerging from the work of many international collaborative groups is that *BRCA1*-associated tumours appear to have a set of clearly defining histological features, such as broad pushing margins and a lymphocytic infiltrate. In contrast, it is difficult to distinguish BRCA2-associated cancers from grade-matched, sporadic breast cancers.

2.2. *BRCA1*

Tumours occurring in *BRCA1* mutation carriers have consistently been found to be most frequently, although not exclusively, negative for the oestrogen receptor (ER) and the growth factor receptor, HER2 but to express basal cytokeratins.[11–13] Gene expression profiling analysis in *BRCA1*-mutated breast tumours concurs, indicating a relative downregulation of ER response genes, upregulation of proliferation associated genes and basal cytokeratins and the lack of high levels of expression of genes in the region of the HER2 gene locus. This expression phenotype leads to the clustering of these tumours with sporadic cancers of basal-like subtype.[14]

Recent data have shed light on the mechanism by which loss of *BRCA1* function might define the lack of ER and ER-regulated gene expression. It seems functional BRCA1 is necessary for the expression of ER alpha by directly binding and transactivating the *ESR1* gene promoter. When BRCA1 is lost in tumours, the ER alpha gene can no longer be expressed and as a result resistance to ER-directed therapy is acquired.[15]

The strong correlation between *BRCA1* status and the so-called ER/ PR/ HER2 negative (triple-negative) and basal-like phenotype should stimulate the ascertainment of a careful family history in women with tumours of this type. There are data to suggest that a combined test using ER and basal keratin status has a higher specificity and better predictive values than clinical algorithms alone. Although independent validation is required, the results of the Breast Cancer Linkage Consortium study suggest that patients with ER negative/basal keratin-positive breast cancers have an odds ratio of approx 148 of having a *BRCA1* mutation when compared to age-matched controls.[12] Even in women with triple-negative breast cancer under forty, where family history is not known, over 20% had a *BRCA1* mutation and this was nearer 30% when a woman under 50 is known to have a strong family history.[16]

2.3. *BRCA2*

Early studies sought to identify defining hallmarks of *BRCA2* breast cancers. Morphological features such as pushing margins and a greater degree of tubule formations were noted but most, including the ER and HER2 status of tumours, were not different from the spectrum of sporadic cancers invasive ductal cancers.[10] However, a recent study has suggested that *BRCA2*-associated tumours are of higher grade with pushing margins, are more frequently ER positive and are less likely to overexpress HER2 compared to control sporadic tumours matched for age and ethnicity. In short, they tend to be a high grade proliferative form of luminal breast cancer.[17]

3. Surveillance and early detection

3.1. *Should BRCA1 or BRCA2 carriers have different breast screening strategies?*

Mammographic screening has become the internationally accepted standard of care for screening women for breast cancer at ages of >40 years. However, breast cancers in mutation carriers are frequently present at a younger age. Furthermore, the data available on the efficacy of mammography as a screening modality in carriers of *BRCA1* or *BRCA2* mutations indicate that tumours are commonly only detected at a high clinical stage and are often present as interval cancers.[18] This is likely to be due to the combination of early onset in a denser breast parenchyma, higher proliferative rate and the broad pushing fleshy morphology of *BRCA1*-associated cancers. This has led six international trials to assess breast MRI in addition to mammographic screening in this group of women. The largest five of these studies have recently been subjected to a combined analysis.[19] Despite the differences in the design and methodology used, some consistent themes emerge. MRI has significantly better sensitivity than mammography alone but this comes at the cost of reduced specificity. The pooled sensitivity and positive predictive value for MRI are 81% and 53% compared to those for mammography that are 40% and 47%.

Although there are no randomised controlled trials of survival outcomes with mammography versus combined MRI and mammography, data are awaited of the comparison of

non-randomised cohorts to historical control cohorts. The evidence that combined approaches detect tumours at <1 cm in 43–67% and with negative nodes in 77–100% of cases strongly suggests that survival benefits can be expected, although a large Dutch trial has recently reported that only 27% of cancers were detected at <1 cm in size and a significant proportion had an involvement of lymph nodes.[20] MRI-based breast screening has already been recommended, with variations in eligible population and recommended age of onset and cessation, for *BRCA1* and *BRCA2* carriers in national and international consensus documents.

3.2. *How can breast cancers be prevented in BRCA1 and BRCA2 carriers?*

There is substantial evidence from a number of both prospective and retrospective studies that the risks of breast cancer can be radically reduced by approximately 90% by bilateral prophylactic mastectomy.[18,21,22] Despite the efficacy of this intervention, the uptake has been found to be less than 30% in women studied.[23–25] Although less effective, prophylatic oophorectomy has also been shown to reduce breast cancer occurrence by approximately 50% and improve breast cancer specific survival when performed in premenopausal women. This effect seems to apply in both *BRCA1* and *BRCA2* carriers, despite the fact that *BRCA1* carriers tend to develop ER negative cancers.[26,27] Despite completion of their family, many women are put off this intervention by the prospect of an early menopause. However, limited data suggest that a period of low-dose hormone replacement therapy may be safe and effective in alleviating menopausal symptoms in women who have not already had a breast cancer.[26]

4. Chemoprevention

The use of tamoxifen for the primary chemoprevention of breast cancer has been studied in women at risk in several studies, but detailed discussion is beyond the scope of this review. A very small number of *BRCA1* and *BRCA2* carriers were identified in the NSABP-P1 study randomising women between tamoxifen and placebo.[28] Although the point estimate for the relative risk of breast cancer suggested some benefit to the use of tamoxifen in the 11 *BRCA2* carriers (RR 0.38; 95% CI, 0.06–1.56) but not in the 8 *BRCA1* carriers studied (RR 1.67; 95% CI, 0.32–10.70), the confidence intervals include unity and cannot be used to inform therapy.

Gronwald et al. examined the secondary preventative effect of tamoxifen on contralateral breast cancer risk in a retrospective matched case-control study in 285 *BRCA1* or *BRCA2* carriers with bilateral breast cancer and in 751 women with unilateral breast cancer and a *BRCA1* or *BRCA2* mutation.[29] History of tamoxifen use was compared between the groups. The multivariate odds ratio (OR) for contralateral breast cancer associated with tamoxifen use was 0.50 (95% CI, 0.30–0.85) for *BRCA1* carriers and 0.42 (95% CI, 0.17–1.02) for *BRCA2* carriers. No protective effect was seen in the very small number of women (16 cases and 123 controls) who had had a prophylactic oophorectomy OR 0.83 (95% CI, 0.24–2.89). Similar effects of tamoxifen in secondary prevention were noted in a recently reported study by Pierce et al.[30] Ten- and 15-year risk of contralateral breast cancer in *BRCA1* and *BRCA2* carriers was 26% (CI, 22–30%) and 39% (95% CI, 31–47%), respectively, compared to that of sporadic controls (3% and 7% risk, respectively). In mutation carriers taking tamoxifen there was a 69% reduction in contralateral breast cancer risk[30] in comparison to mutation carriers who were not treated with tamoxifen (HR 0.31 $p = 0.5$).

Although there are no data from randomised controlled trials in *BRCA1* or *BRCA2* mutation carriers to support the use of tamoxifen, the encouraging nature of these retrospective data should be discussed with carriers who do not wish to undergo prophylactic risk reducing bilateral mastectomy.

4.1. *Does mutation in BRCA1 or BRCA2 influence prognosis?*

This has been a much studied question with a great deal of diversity in both study design and conclusion. Earlier studies were largely based on the analysis of mutation carriers who had been ascertained as a result of inclusion in genetic linkage studies that by their nature were dependent upon having multiple living affected members of the family, thus introducing a bias in favour of improved prognosis in this group. Later studies have in contrast been population based and have usually required confirmation of mutation status by resequencing. A recent publication in this journal[31] has thoroughly reviewed the subject. Despite the methodological heterogeneity and claims of both positive and negative influences of prognosis, the conclusion of this review was that at the time of publication there were no conclusive data that in women with breast cancer *BRCA1* or *BRCA2* mutation status conferred adverse prognosis, other than for contralateral breast cancer occurrence.

Since this review has been published, two other relevant studies have been reported. Moller et al. studied 442 patients who developed breast cancer whilst enroled on prospective breast cancer surveillance programmes because of strong family history of breast cancer. *BRCA1* (89 pts) or *BRCA2* (35 pts) mutation status was confirmed by resequencing. *BRCA1* mutation was associated with worse prognosis even in classical low risk node-negative patients.[32] Rennert et al. conducted a very large population study in Israel in which all new cases of invasive breast cancer in Israel in 1987 and 1988 were sought.[33] Case records and pathology samples were available on 1545 women, and tumour DNA was extracted and analysed for the three Ashkenazi founder mutations in *BRCA1* and *BRCA2*. No difference in overall or breast cancer specific survival was noted for *BRCA1* or *BRCA2* mutation carriers when compared with non-carriers. The adjusted hazard ratio for death from breast cancer did not differ significantly for carriers when compared with non-carriers (hazard ratio for *BRCA1*, 0.76; 95% CI, 0.45–1.30; $P = 0.31$; hazard ratio for *BRCA2*, 1.31; 95% CI, 0.80–2.15; $P = 0.28$). It is worth noting, however, that *BRCA1*-associated breast cancers appear to lose the usual relationship between tumour size and the presence of lymph node metastases.[34]

4.2. *Does BRCA1 or BRCA2 mutation modify response to adjuvant therapy?*

4.2.1. *Adjuvant chemotherapy*

Rennert et al. noted two important observations in the subgroups of their large Israeli study.[33] First, there was a statistically significant interaction between *BRCA1* mutation status and a more favourable prognosis in women receiving adjuvant chemotherapy when compared with non-carriers. Most of these patients had received the CMF regimen in 1987 and 1988. Second, women presenting with tumours less than 2 cm had a worse prognosis if they were *BRCA1* carriers. This is intriguing given the similar results of another retrospective study of similar design conducted in 505 Jewish women in New York and Montreal with small tumours suitable for breast-conserving surgery. Robson et al. found the presence of an Ashkenazi founder mutation in *BRCA1* to be associated with adverse breast cancer survival when compared with non-carriers (62% at 10 years versus 86%; $P < 0.0001$). *BRCA1* status predicted breast cancer mortality only amongst women who did not receive chemotherapy (hazard ratio 4.8, 95% confidence interval 2.0–11.7; $P = 0.001$). Whether this phenomenon relates directly to *BRCA1* gene function or to some other aspect of the basal-like breast cancer phenotype associated with *BRCA1*-mutated breast cancer is not clear. A similar adverse prognosis normalised by an apparent increase in sensitivity to adjuvant chemotherapy in sporadic 'basal-like' breast cancer has also been reported in a small study,[35] and sporadic 'basal-like' breast cancers have been noted to have high response rates to anthracycline-based chemotherapy in common with the other major ER negative subtype, the HER2 positive cancers.[36] There are few data relating to *BRCA1* or *BRCA2* genotype specific effects on normal tissue chemotherapy toxicity. Retrospective data suggest no evidence of increased complications.[37]

Taken together these data suggest that *BRCA1* mutation carriers who present with small and node-negative breast cancers may be at more significant risk of micro-metastatic breast cancer than non-carriers. This may explain a worse prognosis if chemotherapy is avoided in what is regarded as a classically lower risk population. A greater sensitivity to adjuvant chemotherapy, largely CMF in the studies quoted, seems to be correct for any adverse baseline prognosis.

These data, whilst retrospective, may help inform discussions with regard to benefits of adjuvant chemotherapy in carriers with very small node-negative cancers, especially where there seems to be evidence that some of the prognostic significance of pathologically normal lymph nodes seems to be lost in this type of tumour.[34,38] In addition, as current annual MRI and mammography programmes are still detecting most cancers at greater than 1 cm and with node involvement,[20] these data suggest an attenuated impact of early detection imaging programmes on survival end-points for *BRCA1* carriers as it is clear that significant risk of systemic dissemination exists even when lesions are small and node negative at the time of detection.

4.2.2. *Adjuvant radiotherapy following breast-conserving surgery*

A recently published mature analysis of 160 *BRCA1* and *BRCA2* carriers and 445 matched controls treated with breast-conserving therapy and followed for a median of 6–8 years has shown no increase in ipsilateral breast tumour recurrence in carriers who had had a prophylactic oophorectomy when compared to matched controls. An increase was noted in women who did not have prophylactic oophorectomy (HR 1.9, $p = 0.03$).[30] As noted above, contralateral breast cancers were significantly more common in *BRCA1* and *BRCA2* mutation carriers than in controls whether prophylactic oophorectomy was performed or not. Whether the increase in contralateral cancers is due solely to increased baseline risk or due in part to increased radiation carcinogenesis cannot be addressed in this design of study. Of interest, whilst animal studies show an increase in radiation mutagenesis in tissues where both *Brca2* alleles are lost, normal tissues are heterozygous for *Brca2* mutation and show no increase in radiation-induced mutation compared to irradiated wild-type control.[39] Furthermore, there is no evidence of increase in normal tissue radiation toxicity associated with carrier status.[30,40]

4.3. *Are there forms of conventional chemotherapy that are more or less effective in BRCA1/BRCA2-associated breast cancer?*

A number of preclinical studies have been conducted that are informative. The agents that appear to induce greatest genotype specific effect in preclinical models include the DNA cross-linking agents (e.g. carboplatin, cisplatin and mitomycin C).[41–43] These data suggest an increased sensitivity to lesions that damage DNA in ways that arrest, and cause collapse of, DNA replication forks and which subsequently require DNA repair by homologous recombination for fork repair and restart. Such a function is consistent with the integral role that BRCA1 and BRCA2 play in the Fanconi anaemia network,[44] the hallmark of which is exquisite cellular sensitivity to DNA cross-linking agents.

Preclinical experimental data have also suggested that BRCA1 may be required to mediate paclitaxel-induced cell death with the loss of function of BRCA1 leading to microtubule stabilising agent resistance.[45] This has been supported by uncontrolled retrospective data from patients treated with taxane-based neo-adjuvant therapy.[46] The issue of taxane resistance remains controversial as others have found increased sensitivity to taxanes in preclinical BRCA1 deficient models.[47] A UK-based international randomised phase II clinical study is now testing the efficacy of carboplatin and docetaxel in *BRCA1* and *BRCA2* carriers with advanced breast cancer (ISRCTN43372330).

4.3.1. *Targeting BRCA1 or BRCA2 dysfunction with novel therapies*

Exploiting the loss of efficient DNA repair in BRCA1 and BRCA2-deficient tumours, we hypothesised that combining a tumour restricted constitutive defect in homologous recombination with drug-induced inhibition of the base excision and single strand break repair pathways would lead to synthetic lethality restricted to the tumour cell with little effect on normal tissues. Inhibition of poly-ADP ribose polymerase (PARP), a key enzyme in base excision repair, does indeed cause highly selective cell killing in cells that have lost functional BRCA1[48] or BRCA2.[48,49] Cells with defects in other

components of BRCA1, BRCA2 and Fanconi network are also selectively killed.[50] Results obtained in isogenic mouse embryonic stem cell culture systems have been confirmed in tumour cell lines deficient in BRCA1[50] and BRCA2 function[51] and *in vivo* in conditional mouse models[52] and BRCA1 defective spontaneous tumour models.[53]

There has been some debate on the level of sensitivity to PARP inhibitors that loss of BRCA1 or BRCA2 function confers. However, it is now clear that the potency of the PARP inhibitor used is of paramount importance; selective cell killing is not seen for drugs with IC50 for PARP-1 in the micromolar[54,55] rather than in the nanomolar range.[51] In addition, data on the mechanism of resistance to PARP inhibitors and carboplatin in *BRCA2*-mutated cell lines and human cancers provide strong evidence in support of the role played by BRCA1 and BRCA2 inactivation in the sensitivity to these agents (see below).[56]

4.3.2. *Early phase clinical trials of PARP inhibitors in BRCA1 and BRCA2 carriers*

The preclinical results described above stimulated the design of a single agent, first in human, phase 1 study of the Kudos/Astra Zeneca compound AZD2281 in patients with advanced refractory cancers. *BRCA1* and *BRCA2* mutation carriers with advanced refractory cancers were also recruited in later dose escalation cohorts of this study. Initially, the overwhelming majority of *BRCA1* and *BRCA2* carriers had ovarian cancer. Results were presented at the ASCO meeting in 2007[57] and showed linear pharmacokinetics, a favourable toxicity profile dominated by mild nausea and fatigue with evidence of inhibition of PARP in pharmacodynamic analyses in surrogate tissues. This study has now completed accrual of expansion cohorts.

A pair of proof of concept phase II clinical trials using AZD2281 has rapidly followed this phase I study. An advanced ovarian cancer protocol open to BRCA1 and BRCA2 carriers has recently completed accrual. An equivalent advanced breast cancer protocol open to BRCA1 and BRCA2 carriers beyond first-line therapy in the metastatic setting is still in the process of completing accrual (clinicaltrials.gov NCT00494234) at sites in Europe, Australia and the United States (US).

Another single agent PARP inhibitor trial in *BRCA1* and *BRCA2* cancers with advanced breast or ovarian cancers using the Pfizer compound AG014699 is open at sites in the UK sponsored by Cancer Research UK.

4.3.3. *BRCA1 or BRCA2 mechanism-based therapeutic resistance*

Our group has recently studied the mechanisms by which *BRCA2*-mutated cells can acquire resistance to PARP inhibitors and platinum salts. These experiments have shown that mutagenic DNA pathways such as single-stranded annealing,[42] which are upregulated in the absence of BRCA2 function, can drive intragenic deletion events. These can rarely correct the effect of frame shift mutation on the open reading frame and restore the expression of a functional *BRCA2* gene.[56] These rare events may then be selected for over time in a sensitive population. The potential clinical significance of these observations was validated by demonstrating that DNA extracted from an ovarian cancer in a BRCA mutation carrier that had become platinum refractory carried a revertant *BRCA2* allele.[56] These observations suggest that a specific mutation (c.6174delT) in *BRCA2* and sensitivity to therapeutics in cell lines and patients can be suppressed by reversion. The same resistance mechanisms could also occur with other frame shift truncating mutations in either *BRCA1* or *BRCA2* under the selective pressure of treatment with a platinum salt or PARP inhibitor. It is not yet clear which mutations may be more susceptible to this process. However, it seems possible that different mutations may revert at different rates resulting in more or less sustained therapeutic benefit. This issue needs to be further investigated in cohorts of and clinical trials in BRCA mutation carriers.

Correction of a frame shift mutation by intragenic deletion, even when driven by upregulated mutagenic DNA repair mechanisms, is likely to be a rare event which is then selected. The chance of this event occurring is likely to be greater, the greater the bulk of tumour exposed to selective pressure. This argues that if proven active in early phase clinical trials in *BRCA1* and *BRCA2* carriers, platinum salts and PARP inhibitors may have their greatest benefits in low bulk early disease.

4.3.4. *BRCAness*

Although this review concentrates on how germline mutation in *BRCA1* or *BRCA2* might guide therapy choice in breast cancer, much interest has focused on other mechanisms for the loss of function of BRCA1 or BRCA2 function that may exist in breast cancers. This loss of function of genes associated with the DNA damage response predisposes to breast cancer, and has become a common theme in cancer genetics, with mutation in *BRCA1 BRCA2*, *CHEK2* and *PALB2*, all significantly elevating risk.[58] These data suggest that dysregulation of the DNA damage response may occur in a significant proportion of sporadic breast cancers. The overlap between *BRCA1*-mutated cancers and sporadic cancers with basal-like features[14,59] is striking, and a number of recent publications suggest that dysregulation of BRCA1 function via a variety of mechanisms may be a frequent feature of significant subgroups within basal-like breast cancers.[60–63]

5. Conclusion

The identification of the *BRCA1* and *BRCA2* genes rapidly affected the lives of men and women with a very strong family history of breast and ovarian cancers. Until recently, this has largely been restricted to helping and identifying those individuals in some families who are at risk, and to guiding choices about risk-reducing surgery. In recent years, imaging surveillance strategies have evolved that may extend the choice for those who choose to avoid proven benefits of surgery.

The intense efforts paid to understanding the function of BRCA1 and BRCA2 seems at last to promise the potential for new therapies and prevention strategies by turning the consequences of aberrant *BRCA1* or *BRCA2* gene function into tumour-specific targets for synthetic lethal therapy approaches.

Conflict of interest statement

None declared.

REFERENCES

1. Easton DF, Pooley KA, Dunning AM, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature* 2007;**447**:1087–93.
2. Antoniou AC, Easton DF. Models of genetic susceptibility to breast cancer. *Oncogene* 2006;**25**:5898–905.
3. Ashworth A. Oh what a tangled web it weaves: BRCA1 and DNA decatenation. *Cancer Cell* 2005;**8**:95–7.
4. Gudmundsdottir K, Ashworth A. The roles of BRCA1 and BRCA2 and associated proteins in the maintenance of genomic stability. *Oncogene* 2006;**25**:5864–74.
5. Tutt A, Ashworth A. The relationship between the roles of BRCA genes in DNA repair and cancer predisposition. *Trends Mol Med* 2002;**8**:571–6.
6. Santarosa M, Ashworth A. Haploinsufficiency for tumour suppressor genes: when you don't need to go all the way. *Biochim Biophys Acta* 2004;**1654**:105–22.
7. Collins N, McManus R, Wooster R, et al. Consistent loss of the wild type allele in breast cancers from a family linked to the BRCA2 gene on chromosome 13q12–13. *Oncogene* 1995;**10**:1673–5.
8. Cornelis RS, Neuhausen SL, Johansson O, et al. High allele loss rates at 17q12–q21 in breast and ovarian tumors from BRCAl-linked families. The Breast Cancer Linkage Consortium. *Genes Chromosomes Cancer* 1995;**13**:203–10.
9. Merajver SD, Frank TS, Xu J, et al. Germline BRCA1 mutations and loss of the wild-type allele in tumors from families with early onset breast and ovarian cancer. *Clin Cancer Res* 1995;**1**:539–44.
10. Lakhani SR, Gusterson BA, Jacquemier J, et al. The pathology of familial breast cancer: histological features of cancers in families not attributable to mutations in BRCA1 or BRCA2. *Clin Cancer Res* 2000;**6**:782–9.
11. Lakhani SR, Van De Vijver MJ, Jacquemier J, et al. The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. *J Clin Oncol* 2002;**20**:2310–8.
12. Lakhani SR, Reis-Filho JS, Fulford L, et al. Prediction of BRCA1 status in patients with breast cancer using estrogen receptor and basal phenotype. *Clin Cancer Res* 2005;**11**:5175–80.
13. Foulkes WD, Stefansson IM, Chappuis PO, et al. Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer. *J Natl Cancer Inst* 2003;**95**:1482–5.
14. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. *Proc Natl Acad Sci USA* 2003;**100**:8418–23.
15. Hosey AM, Gorski JJ, Murray MM, et al. Molecular basis for estrogen receptor alpha deficiency in BRCA1-linked breast cancer. *J Natl Cancer Inst* 2007;**99**:1683–94.
16. Kandel MJ, Stadler Z, Masciari S, et al. Prevalence of BRCA1 mutations in triple negative breast cancer (BC). *J Clin Oncol (Meeting Abstracts)* 2006;**24**:508.
17. Bane AL, Beck JC, Bleiweiss I, et al. BRCA2 mutation-associated breast cancers exhibit a distinguishing phenotype based on morphology and molecular profiles from tissue microarrays. *Am J Surg Pathol* 2007;**31**:121–8.
18. Hartmann LC, Sellers TA, Schaid DJ, et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. *J Natl Cancer Inst* 2001;**93**:1633–7.
19. Sardanelli F, Podo F, D'Agnolo G, et al. Multicenter comparative multimodality surveillance of women at genetic-familial high risk for breast cancer (HIBCRIT study): interim results. *Radiology* 2007;**242**:698–715.
20. Klijn JG. Mid-term efficacy of a breast cancer screening program for women with a familial or genetic susceptibility: update of the Dutch MRI screening study (MRISC). In: San Antonio breast cancer symposium; 2007 [Abstract 42].
21. Meijers-Heijboer H, van Geel B, van Putten WL, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med* 2001;**345**:159–64.
22. Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic astectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol* 2004;**22**:1055–62.
23. Metcalfe KA, Snyder C, Seidel J, et al. The use of preventive measures among healthy women who carry a BRCA1 or BRCA2 mutation. *Fam Cancer* 2005;**4**:97–103.
24. Uyei A, Peterson SK, Erlichman J, et al. Association between clinical characteristics and risk-reduction interventions in women who underwent BRCA1 and BRCA2 testing: a single-institution study. *Cancer* 2006;**107**:2745–51.
25. Phillips KA, Jenkins MA, Lindeman GJ, et al. Risk-reducing surgery, screening and chemoprevention practices of BRCA1 and BRCA2 mutation carriers: a prospective cohort study. *Clin Genet* 2006;**70**:198–206.
26. Rebbeck TR, Friebel T, Wagner T, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol* 2005;**23**:7804–10.
27. Eisen A, Lubinski J, Klijn J, et al. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. *J Clin Oncol* 2005;**23**:7491–6.
28. King MC, Wieand S, Hale K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. *Jama* 2001;**286**:2251–6.
29. Gronwald J, Tung N, Foulkes WD, et al. Tamoxifen and contralateral breast cancer in BRCA1 and BRCA2 carriers: an update. *Int J Cancer* 2006;**118**:2281–4.
30. Pierce LJ, Levin AM, Rebbeck TR, et al. Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. *J Clin Oncol* 2006;**24**:2437–43.
31. Liebens FP, Carly B, Pastijn A, et al. Management of BRCA1/2 associated breast cancer: a systematic qualitative review of the state of knowledge in 2006. *Eur J Cancer* 2007;**43**:238–57.
32. Moller P, Evans DG, Reis MM, et al. Surveillance for familial breast cancer: differences in outcome according to BRCA mutation status. *Int J Cancer* 2007;**121**:1017–20.
33. Rennert G, Bisland-Naggan S, Barnett-Griness O, et al. Clinical outcomes of breast cancer in carriers of BRCA1 and BRCA2 mutations. *N Engl J Med* 2007;**357**:115–23.
34. Foulkes WD, Metcalfe K, Hanna W, et al. Disruption of the expected positive correlation between breast tumor size and lymph node status in BRCA1-related breast carcinoma. *Cancer* 2003;**98**:1569–77.
35. Rodriguez-Pinilla SM, Sarrio D, Honrado E, et al. Prognostic significance of basal-like phenotype and fascin expression in node-negative invasive breast carcinomas. *Clin Cancer Res* 2006;**12**:1533–9.
36. Rouzier R, Perou CM, Symmans WF, et al. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. *Clin Cancer Res* 2005;**11**:5678–85.

37. Shanley S, McReynolds K, Ardern-Jones A, et al. Acute chemotherapy-related toxicity is not increased in BRCA1 and BRCA2 mutation carriers treated for breast cancer in the United Kingdom. *Clin Cancer Res* 2006;**12**:7033–8.
38. Rakha EA, El-Sayed ME, Green AR, et al. Prognostic markers in triple-negative breast cancer. *Cancer* 2007;**109**:25–32.
39. Tutt AN, van Oostrom CT, Ross GM, et al. Disruption of Brca2 increases the spontaneous mutation rate in vivo: synergism with ionizing radiation. *EMBO Rep* 2002;**3**:255–60.
40. Shanley S, McReynolds K, Ardern-Jones A, et al. Late toxicity is not increased in BRCA1/BRCA2 mutation carriers undergoing breast radiotherapy in the United Kingdom. *Clin Cancer Res* 2006;**12**:7025–32.
41. Moynahan ME, Cui TY, Jasin M. Homology-directed DNA repair, mitomycin-c resistance, and chromosome stability is restored with correction of a Brca1 mutation. *Cancer Res* 2001;**61**:4842–50.
42. Tutt A, Bertwistle D, Valentine J, et al. Mutation in Brca2 stimulates error-prone homology-directed repair of DNA double-strand breaks occurring between repeated sequences. *Embo J* 2001;**20**:4704–16.
43. Bhattacharyya A, Ear US, Koller BH, et al. The breast cancer susceptibility gene BRCA1 is required for subnuclear assembly of Rad51 and survival following treatment with the DNA cross-linking agent cisplatin. *J Biol Chem* 2000;**275**:23899–903.
44. Howlett NG, Taniguchi T, Olson S, et al. Biallelic inactivation of BRCA2 in Fanconi anemia. *Science* 2002;**297**:606–9.
45. Kennedy RD, Quinn JE, Mullan PB, et al. The role of BRCA1 in the cellular response to chemotherapy. *J Natl Cancer Inst* 2004;**96**:1659–68.
46. Byrski T, Gronwald J, Huzarski T, et al. Response to neo-adjuvant chemotherapy in women with BRCA1-positive breast cancers. *Breast Cancer Res Treat* 2008;**108**:289–96.
47. Zhou C, Smith JL, Liu J. Role of BRCA1 in cellular resistance to paclitaxel and ionizing radiation in an ovarian cancer cell line carrying a defective BRCA1. *Oncogene* 2003;**22**:2396–404.
48. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* 2005;**434**:917–21.
49. Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature* 2005;**434**:913–7.
50. McCabe N, Turner NC, Lord CJ, et al. Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition. *Cancer Res* 2006;**66**:8109–15.
51. McCabe N, Lord CJ, Tutt AN, et al. BRCA2-deficient CAPAN-1 cells are extremely sensitive to the inhibition of Poly (ADP-Ribose) polymerase: an issue of potency. *Cancer Biol Ther* 2005;**4**:934–6.
52. Hay T, Jenkins H, Sansom OJ, et al. Efficient deletion of normal Brca2-deficient intestinal epithelium by poly(ADP-ribose) polymerase inhibition models potential prophylactic therapy. *Cancer Res* 2005;**65**:10145–8.
53. Rottenberg S, Nygren AO, Pajic M, et al. Selective induction of chemotherapy resistance of mammary tumors in a conditional mouse model for hereditary breast cancer. *Proc Natl Acad Sci USA* 2007;**104**:12117–22.
54. De Soto JA, Wang X, Tominaga Y, et al. The inhibition and treatment of breast cancer with poly (ADP-ribose) polymerase (PARP-1) inhibitors. *Int J Biol Sci* 2006;**2**:179–85.
55. Gallmeier E, Kern SE. Absence of specific cell killing of the BRCA2-deficient human cancer cell line CAPAN1 by poly(ADP-ribose) polymerase inhibition. *Cancer Biol Ther* 2005;**4**:703–6.
56. Edwards SL, Brough R, Lord CJ. Resistance to therapy caused by intragenic deletion in BRCA2. *Nature* 2008;**451**:1111–5.
57. Yap TA, Boss DS, Fong PC, et al. First in human phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of KU-0059436 (Ku), a small molecule inhibitor of poly ADP-ribose polymerase (PARP) in cancer patients (p), including BRCA1/2 mutation carriers. *J Clin Oncol* 2007;**25**:3529 [Abstract].
58. Johnson N, Fletcher O, Palles C, et al. Counting potentially functional variants in BRCA1, BRCA2 and ATM predicts breast cancer susceptibility. *Hum Mol Genet* 2007;**16**:1051–7.
59. Turner NC, Reis-Filho JS. Basal-like breast cancer and the BRCA1 phenotype. *Oncogene* 2006;**25**:5846–53.
60. Matros E, Wang ZC, Lodeiro G, et al. BRCA1 promoter methylation in sporadic breast tumors: relationship to gene expression profiles. *Breast Cancer Res Treat* 2005;**91**:179–86.
61. Turner NC, Reis-Filho JS, Russell AM, et al. BRCA1 dysfunction in sporadic basal-like breast cancer. *Oncogene* 2007;**26**:2126–32.
62. Abd El-Rehim DM, Ball G, Pinder SE, et al. High-throughput protein expression analysis using tissue microarray technology of a large well-characterised series identifies biologically distinct classes of breast cancer confirming recent cDNA expression analyses. *Int J Cancer* 2005;**116**:340–50.
63. Richardson AL, Wang ZC, De Nicolo A, et al. X chromosomal abnormalities in basal-like human breast cancer. *Cancer Cell* 2006;**9**:121–32.