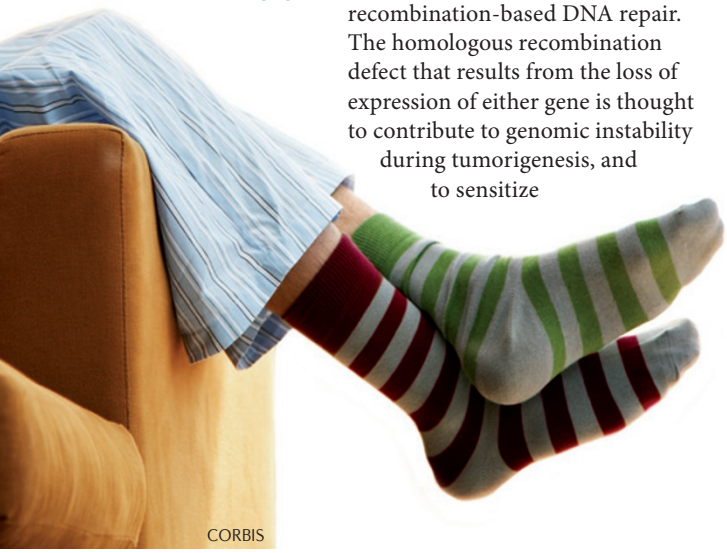
Nature Reviews Cancer | AOP, published online 17 November 2011; doi:10.1038/nrc3177

GENETICS

BRCA inequality

> the outcomes of *BRCA1*-mutated or *BRCA1*-methylated cases were not significantly different from BRCA-wild-type cases



CORBIS

There is a continued debate regarding the clinical predictive value of lesions in *BRCA1* and *BRCA2* in ovarian cancer. A new study suggests that *BRCA1* and *BRCA2* may have more divergent clinical relevance than was previously thought.

Inherited loss-of-function mutations in *BRCA1* or *BRCA2* substantially increase the risk of developing breast or ovarian cancers. Despite having distinct biochemical roles, BRCA1 and BRCA2 are both required for homologous recombination-based DNA repair. The homologous recombination defect that results from the loss of expression of either gene is thought to contribute to genomic instability during tumorigenesis, and to sensitize tumours to therapies, such as platinum agents, that induce the types of DNA damage that are substrates for homologous recombination-based DNA repair.

Wei Zhang and colleagues studied the clinical outcomes of 316 patients with high-grade serous ovarian cancer, who all received surgery followed by platinum-based chemotherapy. Patients were stratified according to the presence of *BRCA1* mutations (37 cases), *BRCA2* mutations (29 cases) or *BRCA1* promoter methylation (33 cases), according to data from The Cancer Genome Atlas (TCGA). For *BRCA1*-methylated samples, *BRCA1* silencing was confirmed at the mRNA level.

The authors found unexpected differences in the clinical predictive value of *BRCA1* versus *BRCA2* lesions when comparing overall survival and progression-free survival (PFS) as primary outcomes and chemotherapy response as a secondary outcome. Whereas *BRCA2* mutations were associated with improved overall survival and PFS, the outcomes of *BRCA1*-mutated or *BRCA1*-methylated cases were not significantly different from BRCA-wild-type cases. *BRCA2* mutations were also associated with an increased rate of response to primary platinum chemotherapy.

In addition, the authors used TCGA exome sequencing data to correlate the genotypes with the extent of accumulated mutations. An increase in genomic instability was found in *BRCA2*-mutated, but not in *BRCA1*-mutated or *BRCA1*-methylated, samples. This could indicate that *BRCA2* lesions cause more substantial homologous recombination defects than *BRCA1* lesions in this disease, because both genomic instability and sensitivity to platinum-based chemotherapy are greater. Overall, such differences led the authors to highlight the need to stratify patients with serous ovarian cancer according to their *BRCA1* and *BRCA2* statuses in future clinical cohorts.

It will be interesting to further investigate the predictive value of *BRCA1* and *BRCA2* lesions in larger patient cohorts, including the biochemical confirmation of BRCA loss of function using homologous recombination assays.

Darren J. Burgess

ORIGINAL RESEARCH PAPER Yang, D. *et al.* Association of *BRCA1* and *BRCA2* mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer. *JAMA* **306**, 1557–1565 (2011)