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Loss-of-function mutations in the BRCA1 and BRCA2 genes increase the risk of cancer. Owing to their function in homologous recombination repair, much research has focused on the unstable genomic phenotype of BRCA1/2 mutant cells manifest mainly as large-scale rearrangements. We used whole-genome sequencing of multiple isogenic chicken DT40 cell clones to precisely determine the consequences of BRCA1/2 loss on all types of genomic mutagenesis. Spontaneous base substitution mutation rates increased sevenfold upon the disruption of either BRCA1 or BRCA2, and the arising mutation spectra showed strong and specific correlation with a mutation signature associated with BRCA1/2 mutant tumours. To model endogenous alkylating damage, we determined the mutation spectrum caused by methyl methanesulfonate (MMS), and showed that MMS also induces more base substitution mutations in BRCA1/2-deficient cells. Spontaneously arising and MMS-induced insertion/deletion mutations and large rearrangements were also more common in BRCA1/2 mutant cells compared with the wild-type control. A difference in the short deletion phenotypes of BRCA1 and BRCA2 suggested distinct roles for the two proteins in the processing of DNA lesions, as BRCA2 mutants contained more short deletions, with a wider size distribution, which frequently showed microhomology near the breakpoints resembling repair by non-homologous end joining. An increased and prolonged gamma-H2AX signal in MMS-treated BRCA1/2 cells suggested an aberrant processing of stalled replication forks as the cause of increased mutagenesis. The high rate of base substitution mutagenesis demonstrated by our experiments is likely to significantly contribute to the oncogenic effect of the inactivation of BRCA1 or BRCA2.