While BRCA1 mutations are known to account for 40–50% of familial breast cancers, an understanding of how they predispose to breast tumorigenesis has been hindered by the lack of a suitable mouse model. Mice heterozygous for a mutation in Brca1 do not develop tumours, and homozygous embryos die early in development. Chu-Xia Deng and colleagues may now have a suitable model; they report, on page 37 of this issue, that mice harbouring a tissue-specific ablation of Brca1 in mammary epithelial cells develop mammary tumours after a long latency period. According to Barry Gusterson, Professor of Histopathology at the Institute of Cancer Research (who has seen slides of the tumour sections), their histopathology is strikingly similar to that of human breast cancer.

The mutants also display abnormalities in mammary morphogenesis, with smaller glands and ducts that fail to penetrate the fat pad (see figure). How, then, can mutations in Brca1 activate growth arrest during the development of mammary tissue and yet trigger unrestrained cell proliferation leading to tumorigenesis later in life? An answer to this apparent conundrum may lie in the proposed role of BRCA1 as a ‘caretaker’, responsible for maintaining genome stability and integrity. In the absence of BRCA1, the accumulation of unrepaired damaged DNA is thought to trigger the action of ‘gatekeepers’, such as p53, leading to a growth arrest response—and this may account for the increased apoptosis observed in the mammary glands of the conditional Brca1 mutant mice. Loss of BRCA1 may set the stage for gradual genome stability ‘melt down’, with mutations manifesting in a multitude of genes, including TP53 (which encodes p53). BRCA1-deficient cells that acquire subsequent mutations in TP53 are anticipated to overcome p53-mediated cell-cycle arrest and undergo unrestrained cell proliferation leading to tumorigenesis. Indeed, Deng and colleagues find that many mammary tumours in the conditional mutant mice harbour gross chromosomal rearrangements, including disruption of Trp53, the mouse homologue of TP53. This is consistent with reports that TP53 mutations are common in human BRCA1 familial breast cancer.

To test whether inactivation of Trp53 contributes to progression of Brca1-associated tumorigenesis, Deng and colleagues introduced a Trp53-null allele into the conditional Brca1 mutant mice and found that tumour formation was accelerated. The majority of tumours had lost the remaining wild-type Trp53 allele, suggesting that inactivation of Brca1 may drive the loss of Trp53. It is likely, however, that the genomic instability arising from Brca1 loss leads to inactivation of several tumour suppressors, which may account for the diverse tumour morphology seen in Brca1 conditional mutant mice and human BRCA1 breast cancer patients.

The conditional mutant mice offer a model to study molecular aberrations arising from Brca1 deficiency, identify genetic modifiers and exogenous factors that influence the onset of tumour formation, and validate potential therapeutic strategies. An indication of how accurately tumour progression in these mice mimics that of human breast cancer patients awaits assessment of whether the tumours are invasive, demonstrate lymph node spread and metastasize to brain, bone, liver and lung—the sites commonly infiltrated in the human disease.

—Carina Dennis