Initiation, evolution, phenotype and outcome of BRCA1 and BRCA2 mutation-associated breast cancer

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We read with great interest the recent Opinion article (BRCA1 and BRCA2: different roles in a common pathway of genome protection. *Nature Rev. Cancer* **12**, 68–78 (2012))¹ by Roy *et al.*, in which the authors present the current knowledge of BRCA1 and BRCA2 in genome protection and cancer development. BRCA1 and BRCA2 are known to function in homologous recombination (HR), and they also function in different stages of the DNA damage response. Notably, the functional roles of BRCA1 and BRCA2 are mainly involved in HR, the alteration of which closely relates to DNA damage-associated breast carcinogenesis but which does not explain the formation of specific breast cancer phenotypes in patients with BRCA1 or BRCA2 mutations. BRCA1-mutated cancer tends to be basal-like, and BRCA2-mutated cancer tends to be luminal-like, although mechanistically there is no convincing evidence that BRCA1 mutation induces basal progenitor cancer cells or that BRCA2 mutation corresponds to luminal progenitor cancer cells at the early stages of carcinogenesis². An important issue, which was not mentioned in the article by Roy *et al.*, is the question of at what time during tumorigenesis do BRCA1 and BRCA2 mutations begin to individually influence breast cancer subtypes.

The authors proposed that hormonally driven growth during each menstrual cycle produces reactive oxygen species (ROS), which cause measurable oxidative DNA damage that is needed for breast carcinogenesis, and which might explain the breast tissue tropism that occurs in women with BRCA1 or BRCA2 mutations. We agree with their speculation that long-term and repeated exposure to ROS, as well as to genotoxic or mutagenic oestrogen metabolites, are important risk factors for breast cancer³. As hormone-associated ROS and oestrogen metabolites are encountered by all normal breast cells regardless of oestrogen receptor (ER) or HER2 status, and as HR is not preferentially activated in different subpopulations of cells in the breast, it seems that BRCA1 and BRCA2 mutations

do not contribute to the formation of breast cancer subtypes at the very beginning of cancer initiation. In addition, the facts that the loss of the wild-type allele of *BRCA1* or *BRCA2* is not required for BRCA1 or BRCA2 mutation-associated breast carcinogenesis⁴, and that common breast cancer susceptibility alleles are also associated with BRCA1 and BRCA2 mutation-associated tumours⁵, consistently suggest that BRCA1 and BRCA2 mutations are not the unique determinants of tumour initiation. In other words, it is the overwhelming levels of hormonally driven ROS and the defective capability of HR, rather than BRCA1 or BRCA2 mutation only, that determine the initiation of carcinogenesis. Instead, the phenotype of BRCA1 and BRCA2 mutation-associated breast cancer, which is probably not determined by levels of ROS and HR capability, might gradually form in the process of cancer evolution rather than at cancer initiation.

Once preneoplastic or cancerous cells form, the ER pathway becomes important in the evolution of ER-positive cancer cells. At this step, BRCA1 and BRCA2 start to show different effects on the evolution of cancer subtypes. Functional BRCA1 is required for ER expression⁶, and BRCA1 also transcriptionally represses the expression of basal-like genes such as cytokeratin 5 (*CK5*), *CK17* and cadherin 3 (*CDH3*)⁷. This

is a potential mechanism to explain the positive association between basal markers and BRCA1-deficient tumours. As *BRCA1* is frequently either mutated or methylated in most hereditary and sporadic breast cancer^{8,9} (although the timing of *BRCA1* methylation is unclear), the BRCA1 mutation-associated or low expression-associated cancer tends to evolve a basal-like subtype^{10,11}. For BRCA2, which can be transcriptionally regulated by ER¹², the precise mechanism through which BRCA2-mutated cancer cells finally develop to luminal-like subtype (ER-positive) tumours is unknown.

Theoretically, different phenotypes of breast cancer might lead to altered outcomes. In Table 3 of their article¹, the authors stated no difference in prognosis between BRCA1- and BRCA2-mutated cancer and sporadic cancer at the same stage. However, studies exhibit inconsistent results (TABLE 1). A meta-analysis showed that BRCA1 mutation decreases short-term and long-term overall survival and short-term progression-free survival, but BRCA2 mutation does not affect either¹³. The difference in prognosis between BRCA1 and BRCA2 mutation-associated tumours could be due to the difference in clinical phenotype. Another new prospective population-based cohort study showed that the outcomes of BRCA1-mutation carriers were similar to those of patients with sporadic breast cancer, whereas the risk of death was higher in BRCA2-mutation carriers relative to sporadic cases before adjustment¹⁴. Interestingly, a pooled analysis showed that BRCA2-mutation carriers with invasive epithelial ovarian cancer have a more favourable survival even when compared with BRCA1-mutation carriers¹⁵. Because of the inconsistent results in prognosis for BRCA mutation-associated cancers, future data from large prospective cohort studies are warranted.

Table 1 | Meta-analyses of BRCA mutation-associated cancer and prognosis

Cancer type	Design	Number of patients with BRCA1 mutation, BRCA2 mutation or non-carriers	Patients with BRCA1 mutation versus non-carriers OR (95% CI)	Patients with BRCA2 mutation versus non-carriers OR (95% CI)	Survival
Breast cancer	Meta-analysis ¹³	BRCA1 501 BRCA2 269 Non-carriers 3,154*	1.92 (1.45–2.53)	1.30 (0.95–1.76)	Short-term OS (4–5 years)
Breast cancer	Meta-analysis ¹³	BRCA1 501 BRCA2 269 Non-carriers 3,154*	1.33 (1.12–1.58)	1.12 (0.86–1.45)	Long-term OS (10–20 years)
Invasive EOC	Pooled analysis ¹⁵	BRCA1 909 BRCA2 304 Non-carriers 2,666	0.73 (0.64–0.84)	0.49 (0.39–0.61)	Adjusted 5-year OS

CI, confidence interval; EOC, epithelial ovarian cancer; OR, odds ratio; OS, overall survival. *Total number of subjects of the meta-analysis (excluding sporadic cases).

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1. Roy, R., Chun, J. & Powell, S. N. BRCA1 and BRCA2: different roles in a common pathway of genome protection. *Nature Rev. Cancer* **12**, 68–78 (2012).
2. Molyneux, G. & Smalley, M. J. The cell of origin of BRCA1 mutation-associated breast cancer: a cautionary tale of gene expression profiling. *J. Mammary Gland Biol. Neoplasia* **16**, 51–55 (2011).
3. Yager, J. D. & Davidson, N. E. Estrogen carcinogenesis in breast cancer. *N. Engl. J. Med.* **354**, 270–282 (2006).
4. King, T. A. *et al.* Heterogenic loss of the wild-type BRCA allele in human breast tumorigenesis. *Ann. Surg. Oncol.* **14**, 2510–2518 (2007).
5. Mulligan, A. M. *et al.* Common breast cancer susceptibility alleles are associated with tumour subtypes in BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2. *Breast Cancer Res.* **13**, R110 (2011).
6. Hosey, A. M. *et al.* Molecular basis for estrogen receptor alpha deficiency in BRCA1-linked breast cancer. *J. Natl Cancer Inst.* **99**, 1683–1694 (2007).
7. Gorski, J. J. *et al.* BRCA1 transcriptionally regulates genes associated with the basal-like phenotype in breast cancer. *Breast Cancer Res. Treat* **122**, 721–731 (2010).
8. Birgisdottir, V. *et al.* Epigenetic silencing and deletion of the BRCA1 gene in sporadic breast cancer. *Breast Cancer Res.* **8**, R38 (2006).
9. Pang, D. *et al.* Methylation profiles of the BRCA1 promoter in hereditary and sporadic breast cancer among Han Chinese. *Med. Oncol.* **11** Nov 2011 (doi:10.1007/s12032-011-0100-0).
10. Foulkes, W. D. *et al.* Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer. *J. Natl Cancer Inst.* **95**, 1482–1485 (2003).
11. Stefansson, O. A. *et al.* CpG island hypermethylation of BRCA1 and loss of pRb as co-occurring events in basal/triple-negative breast cancer. *Epigenetics* **6**, 638–649 (2011).
12. Jin, W. *et al.* Estrogen receptor (ER) β or p53 attenuates ER α -mediated transcriptional activation on the BRCA2 promoter. *J. Biol. Chem.* **283**, 29671–29680 (2008).
13. Lee, E. H. *et al.* Effect of BRCA1/2 mutation on short-term and long-term breast cancer survival: a systematic review and meta-analysis. *Breast Cancer Res. Treat* **122**, 11–25 (2010).
14. Goodwin, P. J. *et al.* Breast cancer prognosis in BRCA1 and BRCA2 mutation carriers: an International Prospective Breast Cancer Family Registry population-based cohort study. *J. Clin. Oncol.* **30**, 19–26 (2012).
15. Bolton, K. L. *et al.* Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. *JAMA* **307**, 382–390 (2012).

Competing interests statement

The authors declare no competing financial interests.