A decade of discovery of BRCA1 and BRCA2: Are we turning the tide against hereditary breast cancers?

Hereditary cancer accounts for 3-5% of all breast cancers and a greater proportion of ovarian cancers. However by virtue of breast cancer being so prevalent, every year tens of thousands of women worldwide develop breast or ovarian cancer due to inherited predisposition. In addition, hundreds of thousands of healthy women worldwide are likely to be harbouring germline mutations in breast cancer predisposing genes, which carry a 50-80% life-time risk of developing these cancers. This underscores the need for understanding the biological basis of this condition and to develop effective strategies for prevention, early detection and better management of hereditary breast cancer. In the early nineties when the 1st Breast Cancer gene - termed BRCA1 (Miki et al, Science, 1994) and the 2nd Breast Cancer gene - termed BRCA2 (Wooster et al, Nature, 1995), were identified as the cause of genetic predisposition in hereditary breast and breast ovarian cancers, it was hailed as a major scientific discovery. While this discovery had a cascade effect on basic biology and genetics research, the wider community of clinicians and oncologists are still unsure of the clinical utility of such genetic testing and whether the benefits, if any, would outweigh the psycho-social distress associated with genetic testing. The problem was compounded by lack of specialized genetic clinics where these patients could be referred for evaluation and counseling and the limited availability and cost of mutation analysis. However, within a decade of this discovery, several aspects of prevention, diagnosis and treatment of BRCA1/2 associated cancers have changed. Much of this change has come as a result of better understanding of the biological underpinnings of such cancers and through collaborative consortium mode research.

Firstly the discovery of these two tumour suppressor genes fuelled further basic and genetic research resulting in better understanding of the mechanism underlying hereditary breast cancer as well as more reliable genotype-phenotype correlations. Important geo-ethnic variations in the frequency and spectrum of BRCA1/2 mutations were reported and several founder mutations in the Ashkenazi Jewish, Icelandic and some other populations have now been identified. Recently some novel germline BRCA1/2 mutations have been reported in breast cancer patients from India, Iran, Pakistan and several other Asian geo-ethnic groups. There are different methods of screening for mutations in these two large genes, each with different sensitivity and specificity and the mutation should be confirmed with direct sequencing. However all sequence variations in BRCA1/2 may not be pathogenic - some being well-characterized, harmless polymorphism and others of unknown significance. In contrast to women of Jewish or other Caucasian descent, the relatively much smaller Caucasian database of women from other ethnic groups makes it more difficult to interpret the results of mutation analysis in these populations. This underscores the need to establish a comprehensive database of pathological mutations and polymorphisms in BRCA1 and BRCA2 genes in different geo-ethnic groups of not only cancer-affected persons with suspected inherited predisposition but also of their healthy controls from the same geo-ethnic groups.

Such families with inherited predisposition have special needs for the assessment of cancer risk and advice regarding the advantages and limitations of genetic testing, best strategy for screening, prevention and therapy of cancer. In the past decade, most cancer centres in North America and Europe have either set-up specialized high risk or cancer genetics clinic in their centres or a established a referral network. However in India clinical genetic services and counseling for hereditary cancers is a nascent field with only two such cancer genetics clinics, one at our centre and another at Cancer Institute (WIA), Adyar, Chennai. The importance of counselling is highlighted in a meta-analysis of 10 randomised trials (Meiser and Halliday, Soc Sci Med. 2002) showing that genetic counseling significantly
decreased generalized anxiety, although the reduction in psychological distress was not significant.

Unlike sporadic breast cancers, hereditary breast cancer can occur at a much younger age and with a high propensity for multifocal involvement and bilateral cancer. In such women, breast cancer screening is indicated from a much younger age. As expected, due to dense breasts in these young women, clinical examination, mammography and sonography all have quite low sensitivity of below 50%. Several recent studies, including the UK MARIBS study group (Lancet, 2005) have shown that MRI has much higher sensitivity of 75% or more for detecting breast cancer among women with a BRCA1/2 mutation as compared to mammography, clinical breast examination or ultrasonography.

The options for cancer prevention in these high-risk women include chemoprevention using tamoxifen or similar agents and prophylactic mastectomy or prophylactic oophorectomy. Few large retrospective studies, the prospective PROSE study and the 2004 Cochrane review meta-analysis all show a consistent 85% to 100% reduction in long-term risk for breast cancer development with prophylactic bilateral mastectomy in women at high-risk of developing hereditary breast cancer. Subcutaneous mastectomy, which leaves behind the nipple and areola, may have a slightly higher risk of future cancer development as opposed to total mastectomy. However, for healthy young women, subcutaneous mastectomy with breast reconstruction is more acceptable than total mastectomy with reconstruction as it is cosmetically superior. Bilateral prophylactic oophorectomy not only reduces the risk of ovarian cancer by over 95% but also the risk of breast cancer by 50%.

The differences in the natural history, presentation and underlying biological defect in hereditary breast cancers as opposed to the sporadic cancers have certain implications for their optimal loco-regional and systemic treatment. We now know that BRCA1/2 associated breast cancers have a distinct genetic signature of Basal Type with preponderance of poorly differentiated ER, PR and HER2-neu negative tumours. Few reports, including one from Yale University showing 49% ipsilateral breast recurrence rate at 13 years after Breast Conservation Therapy (Haffty et al, Lancet 2002) had raised serious concern about the safety of this treatment approach in young women with hereditary breast cancer. However the largest multi-institutional report (Pierce et al, JCO 2006) found no excess ipsilateral breast recurrence rate at 10 years in 170 women with germline BRCA mutation (12.5%) as compared to 469 matched women with no germline BRCA mutation (8.6%). Nevertheless, BCT should be offered with caution to young women with hereditary cancer, ensuring that their breast imaging is sensitive enough to rule out multicentric involvement.

The most exciting development to tackle this malady has finally come through better insight in its biology. Novel approaches for enhanced anti-tumour effect are being clinically tested in women with hereditary breast cancer to exploit the inherent defect in the DNA damage repair in their cancer cells as a result of BRCA1/2 mutation. In some other cancers, molecules or receptors that drive the growth of tumour are targeted or blocked as in the case of CML (Imatinib), HER2 positive breast cancer (Trastuzumab) and lung / head and neck cancers (Gefitinib). In contrast, in BRCA1/2 associated cancers, the inherent weakness of genetic instability arising from germline mutations in these tumour suppressor genes, which in the first place caused cancer, can be targeted to enhance the anticancer effect of specifically chosen cytotoxic agents or with novel targeted therapies. Defect in repair of DNA double strand break makes these tumours more sensitive to the platinum compounds and a clinical trial of carboplatin in such patients is ongoing. Based on the finding that inhibitors of poly ADP-ribose polymerase (PARP) result in the death of tumour cells with BRCA1/2 dysfunction by causing marked chromosomal instability and apoptosis, a phase I clinical trial of PARP inhibitor has been started in women with BRCA1/2 associated hereditary breast cancer.

The progress made within a decade of the discovery of BRCA1 and BRCA2 genes does indicate that we are slowly but surely turning the tide against this not so common yet important malady. A success story with PARP inhibitors in BRCA1/2 associated cancers would show us the way of turning misfortune into escape routes and forcing foes to turn friends.