Abstract

Management of Breast Cancer in BRCA1/2 Mutation Carriers

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About 10% of breast cancer cases occur in individuals who have inherited a high-risk breast cancer predisposition gene. Individuals in this situation have inherited one altered copy of a cancer predisposition gene which markedly increases risk of cancer at certain sites, although cancer will not definitely occur. This is because at least one second genetic event has to occur either in the remaining normal copy or in other genes which control cellular genetic stability. This has several implications for the management of cancer in gene carriers:

- After a breast cancer diagnosis, such individuals may be at risk of a new primary tumour, for example a BRCA1 carrier has a 64% and a BRCA2 carrier a 56% lifetime risk of a second primary breast tumour (Breast Cancer Linkage Consortium data). There is currently debate as to whether such patients should be treated with bilateral mastectomy.

- Individuals may be at increased risk of cancers in other sites, for example female BRCA1 carriers are at increased risk of ovarian cancer. A BRCA1 carrier who has had breast cancer may therefore need screening for ovarian cancer.
- Certain cancer predisposition genes are involved in the repair of DNA damage, for example TP53 carriers in Li-Fraumeni families are more likely to accumulate and tolerate DNA damage if exposed to radiation or chemotherapy. This increases the risk of second tumours. Such patients may be better managed by surgery rather than DNA damaging agents. In collaboration with Dr. Camplejohn at St. Thomas' Hospital, London, we have studied resistance to apoptosis in blood lymphocytes in carriers and non-carriers of the TP53 gene and have shown that in TP53 carriers there is resistance to apoptosis following radiation. Early data related to BRCA1/2 carriers do not show any obvious resistance to apoptosis, but more samples need to be studied. There is no early indication of differences between BRCA1/2 carriers and controls. Early data on clonogenic survival of normal skin fibroblasts from 6 BRCA1 carriers and 19 non-carriers to assess radiosensitivity and pulse field gel electrophoresis to assess repair of DNA damage between BRCA1 mutation carriers and controls do not show any difference. However, more data are needed and defects in repair in tumour cells with a double genetic event may be different.