

Radiation and Chemotherapy Side Effects in BRCA1/2 Mutation Carriers.

Sue Shanley, The Royal Marsden NHS Trust

Background

This study analysed whether conventional therapy for breast cancer presents an elevated risk to normal tissue in BRCA1/2 mutation carriers. Current screening methods involve ionising radiation and treatment involves ionising radiation and DNA-damaging chemotherapeutics. Therefore it is important to establish whether there is increased toxicity in these individuals and thus determine the best way to screen and treat breast cancer in this group.

Previous studies

BRCA1/2 proteins have an integral role in homologous recombination DNA repair. In vitro data suggest that BRCA1/2 null cells have increased radiosensitivity. Data from heterozygous cells is less conclusive, although overall there is thought to be some radiosensitive phenotype. There are few molecular data for the effect of chemotherapy on BRCA1/2 null cells.

Studies to investigate whether the increased sensitivity observed in vitro translates into a clinical effect are scarce for radiotherapy and there are none on chemotherapy at present.

Study outline

This study documented the UK experience of breast radiotherapy and chemotherapy in BRCA 1/2 carriers treated for breast cancer. Fifty-five subjects being treated with radiotherapy were recruited alongside 55 case matched controls. Thirty-four of the subjects also had chemotherapy and an additional 28 were recruited who had chemotherapy treatment alone. Controls were individuals with sporadic breast cancer. Matching was very challenging due to the large number of factors that needed to be considered including age, time since treatment, stage of tumour, type of therapy etc. The chemotherapy regimens could not be matched in all cases.

Radiotherapy toxicity

Following radiotherapy, the acute toxicity outcomes were a reported increased breast pain in carriers (although this was not supported by clinical records). For chronic toxicity there were no significant differences between cases and controls. Patients were also evaluated using the LENTSOMA system, which is a 12 item scale based upon patient reporting systems and objective analysis through examination. In addition clinical photographs were used to score for changes in breast shape and skin coloration. The distribution of scores was the same in cases and controls for both evaluations.

Overall there was no demonstrable increase in late toxicity in BRCA carriers exposed to radiation treatment.

Chemotherapy toxicity

For chemotherapy, toxicity was evaluated using the ECOG criteria. CMF and FEC were the main regimens used for patients in the study and there was a bias towards BRCA1 carriers having the greatest exposure to the CMF regimen. No toxicity was witnessed in BRCA2 carriers whilst levels in BRCA1 carriers were similar to that in controls. This is likely to reflect the difference in treatment regimens rather than genetic status. The most common side effect observed was neutropenia, which normally led to a reduction in dosage.

No increase in toxicity in normal tissues was detected in carriers treated with chemotherapeutic agents.

Conclusions

In conclusion this was the first UK study to make detailed assessments of the effects of radiotherapy treatment in BRCA1/2 carriers. It was limited by matching constraints – any differences less than 20% between cases and controls would not have been detected.

Overall there is no indication that normal tissue in BRCA1/2 carriers is at increased risk of toxicity from current radiotherapy and chemotherapy treatment regimens.