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Tamoxifen for primary breast cancer prevention in *BRCA* heterozygotes

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1. Introduction

Female reproductive hormones appear to be involved in the development of hereditary breast cancer associated with germline *BRCA* mutations. First, breast cancer is relatively uncommmon in males with *BRCA* alterations. Data from the Breast Cancer Linkage Consortium (BCLC) indicate a risk of 6.92% by age 70 years for males with *BRCA2* mutations, compared with a 40.6% risk for females [1]. Second, in women the risk is greater in premenopausal women. At Memorial Sloan-Kettering Cancer Center (MSKCC), approximately 75% of *BRCA1*-associated and 66% of *BRCA2*-associated breast cancers are diagnosed before the age of 50 years. Third, risk-reducing oophorectomy and the induction of premature menopause has been reported to be associated with a 47% (95% Confidence Interval (C.I.) 16–67%) reduction in breast cancer risk in *BRCA1* carriers [2]. Finally, pregnancy has been associated with an increased risk of early-onset cancer in carriers [3,4] which may be mediated by elevated oestrogen levels.

2. Do anti-oestrogens work?

The above observations suggest that antagonism of oestrogenic action on the breast could be an effective prevention strategy for hereditary breast cancer. The hypothesis was supported by a case–control study from the Hereditary Breast Cancer Clinical Study Group [5]. In this study, 209 women who had bilateral breast cancer and known deleteroius *BRCA* mutations were compared with 384 matched *BRCA* heterozygotes with unlateral breast cancer. Tamoxifen (T) was used by 64 (13%) of *BRCA1* mutation carriers and 39 (33%) *BRCA2* mutation carriers. In multivariate analysis, T use(ever/never) was associated with a 50% reduction in the risk of developing bilateral breast cancer (95% C.I. 0.28–0.89), with benefit being observed in both *BRCA1* and *BRCA2* carriers. Increasing benefit was observed up to 4 years of use, but no significant risk reduction was seen with longer durations, although the numbers of cases and controls were small.

With these data in hand, it was hoped that studies of T use in unaffected women with mutations would confirm the benefit observed in affected individuals. To this end, an analysis was performed of women participating in the US Breast Cancer Prevention Trial (BCPT) [6]. Of the 320 study participants who developed breast cancer, *BRCA1/2* mutation analysis was performed on 288, of whom 19 (6.6%) were found to have deleterious mutations [7]. Of the patients developing breast cancer with *BRCA1* mutations, 3 were taking placebo and 5 tamoxifen (risk ratio 1.67; 95% C.I. 0.32–10.70). Of the 11 breast cancer patients with *BRCA2* mutations, 8 were taking placebo and 3 were taking tamoxifen (risk ratio 0.38; 95% C.I. 0.06–1.56). While these results did not indicate any significant benefit for the use of T, there was a suggestion of benefit in women with *BRCA2* mutations.

There are several hypotheses that may explain the discordant results of the BCPT subset analysis and the Hereditary Breast Cancer Clinical Study Group case–control study. Most obviously, despite the large size of the BCPT, the power to detect differences in mutation carriers is low because of the rarity of *BRCA* mutations. Relevant benefits could easily be missed in what is effectively a randomised study of 19 women. Women with mutations in *BRCA1* and *BRCA2* may also respond differentially to T. It is well known that *BRCA-1* associated breast cancer is very likely to be oestrogen-receptor (ER)-negative, while *BRCA2*-associated disease is often positive. In a recent review, 51/285 (17.9%) cases of *BRCA1*-associated breast cancer were ER-positive, compared with 66/98 (67.3%) cases of

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BRCA2-associated cancer [8]. Since T was ineffective in reducing the risk of ER-negative cancer in the BCPT, the inability of the agent to reduce risk in unaffected *BRCA1* carriers is perhaps not unexpected. Why the drug appeared to be effective in reducing contralateral cancer risk in affected *BRCA1* carriers is unclear. One may speculate that a significant proportion of *BRCA1* carriers who received T in the case–control study did so either because they were postmenopausal or because their first cancer was ER-positive, despite the fact that neither condition is common among affected *BRCA1* carriers. Older *BRCA1* carriers may be more likely to develop ER-positive disease and thus may be more likely to benefit from T [9]. In addition, several studies in sporadic cancer have suggested that the receptor status of a contraleteral breast cancer may not be completely independent from the first. Thus, women with ER-positive initial cancers may be more likely to develop ER-positive contralateral disease, and would be expected to experience a greater T-related reduction in second cancer risk despite their genotype. Of course, confounding of the case–control analysis by uncorrected selection bias or unanticipated factors may also have played a role.

3. Conclusion

In conclusion, then, currently available evidence neither supports nor refutes the hypothesis that tamoxifen may be of use in reducing hereditary cancer risk, at least among a subset of *BRCA* heterozygotes. Until further data become available, women should be encouraged to enroll on clinical trials studying this question. *BRCA* heterozygotes with ER-positive breast cancer should continue to receive T to reduce the risk of recurrence of their established disease.

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