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Regarding the Use of Tamoxifen Post-Oophorectomy to Prevent Hereditary Breast Cancer

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Options for the prevention of breast cancer in carriers of a *BRCA1* or *BRCA2* mutation include oophorectomy and tamoxifen [1]. It is possible to reduce the risk of breast cancer by 60% by performing surgical menopause at age 40 or before [2]; however, given the projected lifetime risk of 80% and penetrance of 30% by age 40, this leaves a residual risk post-oophorectomy of 30%. What can be done to reduce this risk? A healthy diet should be recommended [3] but surely it is optimistic to assume that risk can be managed by diet alone. There is interest in the potential use of aromatase inhibitors in chemo-prevention, but none have yet been approved in this setting, and their side effects have not yet been fully evaluated. Raloxifene and tamoxifen appear to have equivalent effects in chemoprevention in women at average or medium risk [4], but raloxifene has not been studied in mutation carriers. Tamoxifen has been shown to reduce the risk of contralateral and ipsilateral breast cancer in several studies of *BRCA1* and *BRCA2* carriers [5-8]. Few would dispute that oophorectomy should be recommended by age 40 to reduce the risk of breast and ovarian cancer, but there is no consensus on the use of tamoxifen – and its use is not widespread. There are some data on the joint effect of tamoxifen and oophorectomy in women with *BRCA1* and *BRCA2* mutations – this is all based on evaluating the risks of contralateral breast cancer. Unfortunately, we should not expect data on primary prevention with tamoxifen any time soon. Therefore, it is important to examine the published data on contralateral risk.

Metcalfe et al. conducted a historical cohort study on 491 women with a *BRCA1* or *BRCA2* mutation who were followed for contralateral breast cancer [6]. The combination of tamoxifen and oophorectomy was particularly effective in women under 50; the hazard ratio associated with this combination of therapy was 0.09 (95% CI, 0.01 to 0.68; $P=0.02$).

In a matched case-control study, Gronwald et al. studied 285 women with bilateral breast cancer and a *BRCA1* or *BRCA2* mutation, and 751 control women with unilateral breast cancer and a *BRCA1* or *BRCA2* mutation [7]. The use of tamoxifen for treating the first breast cancer was compared between bilateral and unilateral cases. The multivariate odds ratio for contralateral breast cancer associated with tamoxifen use was 0.50 for carriers of *BRCA1* mutations and was 0.42 for carriers of *BRCA2* mutations. However, in contrast to Metcalfe's study, the protective effect of tamoxifen was not present among women who had undergone an oophorectomy ($OR=0.83$). However, this subgroup was small and the confidence interval was wide (95%CI, 0.24-2.89). A strong protective effect of tamoxifen was apparent among women who had undergone natural menopause ($OR=0.44$; 95% CI, 0.27-0.65).

Should tamoxifen be given to women with mutations who have had an oophorectomy? Clearly, more data are needed. In women over 50, or who had an oophorectomy after natural menopause, tamoxifen should be effective. In young women (<50) following surgical menopause, the data are less clear-cut, but I think the drug should be considered. Factors to take into consideration when making this decision should include the estimate of the residual lifetime risk of cancer, the woman's level of interest in mastectomy (there is no point in giving tamoxifen to healthy women after prophylactic mastectomy), the presence of an intact uterus (i.e., risk of endometrial cancer) and access to MRI screening facilities.

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