S30. The Importance of Estrogen Withdrawal in Breast Cancer Prevention

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Epidemiological studies demonstrate that ovarian ablation (OA) at about age 40 reduces the subsequent incidence of breast cancer by half and that the earlier in life OA occurs the greater the reduction in risk. These data in women at population risk are supported by OA in BRCA-1 or BRCA-2 carriers where a similar degree of risk reduction is seen. The reduction in BRCA-1 carriers who develop mainly estrogen receptor (ER) negative tumours suggests that prevention acts via a precursor breast lesion which is ER positive. In postmenopausal women estrogen withdrawal by inhibition of the aromatase enzyme results in reduction of relapse by more than 20% and a reduction of new contralateral breast cancers (CBC) by approximately 50% in trials where aromatase inhibitors (AIs) were compared with tamoxifen. Since tamoxifen is known to reduce CBCs by approximately 50% compared to placebo, AIs may reduce breast cancer incidence by 70-80% compared with placebo as judged by cross trial comparisons (data from the ATAC, IES & BIG1-98 studies and the EBCTCG overview). Two randomised trials of AIs in postmenopausal women at risk are in progress. One compares anastrozole with placebo (IBIS II) and the other exemestane with placebo (MA3). The trials will recruit 6,000 and 5,000 patients respectively and each has subprotocols to assess the effect of AIs on bone density and cognitive function and other parameters.

It is likely that the AIs will be superior to placebo in the above trials and may also be superior to tamoxifen. However, there are major unanswered questions with respect to estrogen withdrawal on the breast including the target structures within the breast and why not all breast cancers are prevented. In premenopausal women estrogen withdrawal reduces proliferation in normal lobules whereas in postmenopausal women these have atrophied and are largely non-proliferative in the lowered estrogen environment after the menopause. Experimental data suggests that changes which allow lobules to proliferate in a low estrogen environment include increase in the number of ER +ve cells, loss of the separation between ER +ve and proliferating cells and lack of suppressive TGFβ. Resistance to OA and AIs may be related to loss of ER or activation of ER via membrane and growth factor pathways as seen in overt tumours in a low estrogen environment. This suggests that new prevention strategies should include estrogen suppression and inhibition of growth factor pathways.