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Written report of presented lectures: endocrine treatment and prevention of breast and gynaecological cancers: The scientific basis of endocrine prevention

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The science of endocrine prevention is based on the cell and molecular biology of the mammary gland and the epidemiology surrounding the development of breast cancer. The major epithelial structures of the breast are the ducts and the lobules. Each lobule comprises two epithelial cell layers, luminal epithelial cells which differentiate under hormonal influences to produce milk during and after pregnancy and basal myoepithelial cells which contain smooth muscle actin and have contractile properties. Experiments where low numbers of tagged mouse epithelial cells are transplanted to the mammary fat pad suggest that the mammary gland can be derived from a single stem cell [1]. Some transplanted epithelial cells give rise to ducts only or lobular-like structures only indicating that there are committed progenitor cells for each of these structures [2]. A proportion of single epithelial cells (~5%) when dissociated from the reduction mammoplasty tissue give rise to colonies which contain cells with markers for both luminal and myoepithelial cells suggesting a single progenitor for both cell types [3]. There is also evidence for a proliferating transit population of cells between the single precursor cell and differentiated luminal and myoepithelial cells. Luminal epithelial cells are of at least two types based on their oestrogen receptor (ER) status. The nucleus of approximately 20% of cells stains with antibodies to ER using immunocytochemical methods. These same cells also contain progesterone receptors (PR). However, the cells which express ER and PR are differentiated and rarely divide and it is probable that oestrogen and progesterone exert their proliferative effects by inducing paracrine growth factors which produce their proliferative effects on adjacent ER/PR-negative cells [4,5]. There is evidence that the separation between ER/PR-positive steroid hormone sensor cells and ER/PR-negative effector cells is reduced with age, indicating a transit population of ER/PR-positive proliferative cells which could potentially be targets for carcinogenesis. It is known that the numbers of ER/PR-positive proliferating cells are markedly increased in ER-positive breast cancers and moderately increased in hyperplasia of usual type and atypical ductal hyperplasia [6]. Thus, as the female ages, ER/PR-positive proliferating cells can be detected suggesting that these cells may be a target for malignancy and that this population of cells expands in ER-positive premalignant and malignant lesions. Rats treated with the carcinogen methylnitrosurea (MNU) show increased numbers of ER/PR-positive proliferating cells and this increase can be prevented by mimicking pregnancy with high-dose oestrogen and progesterone for 21 days before the administration of MNU [7]. The data outlined above suggest a model for the action of preventive endocrine therapy. Wellings and colleagues [8] and others suggest that breast cancer arises in a terminal duct/lobular unit. Under normal circumstances, these units comprise a series of progenitor cells which give rise to luminal (ER/PR-positive and -negative) and myoepithelial cells. The control of cell production of cell types is probably regulated by feedback to the progenitor cell from the ER/PR-positive sensor cell. Preventive endocrine therapy (e.g. Selective Oestrogen Receptor Modulators (SERMs) or ovarian ablation) given under these normal circumstances would reduce proliferation (and

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putatively) malignant transformation in ER-positive and ER-negative cells by a feedback mechanism, thus potentially suppressing all tumour types. However, if preventive endocrine therapy is given after the early stages of malignancy have developed, lesions with a predominant ER/PR-positive phenotype will be suppressed, whereas those with an ER-negative phenotype will not. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) P1 tamoxifen prevention trial and the raloxifene prevention trial (MORE), only ER/PR-positive tumours were prevented suggesting that treatments were suppressing early malignancy rather that preventing it. Attempts to induce differentiation by, for example, mimicking pregnancy using chorionic gonadotrophin (HCG) or high-dose reproductive [9] steroids may be effective when lobules are normal, but relatively ineffective after the malignant process has been initiated since induction of differentiation in mammary tumours has proved to be difficult. Follow-up data of women given oophorectomy in their thirties or early forties for benign conditions and the results of P1 and MORE studies indicate that approximately one-half of tumours are prevented or suppressed. Elimination of the other half may require endocrine measures to be implemented at an earlier age.

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