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How do endogenous oestrogens affect breast cancer?

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The major epidemiological risk factors for breast cancer such as gender, age parity, age at first baby, height and weight relate to endogenous oestrogen exposure, with the exception of age and height. The variety of tumour types and different phenotypes Oestrogen Recepter (ER), Progesterone Receptor (PR), c-erb2) argue against breast cancer evolving as a homogeneous entity. Oestrogenic promotion will have no impact on ER-tumours. Prevention trials with Selective Oestrogen Receptor Modulators (SERMs), National Surgical Adjuvant Breast and Bowel Project (NSABP), P1 and Multiple Outcomes of Raloxifene Evaluation (MORE), showed a 70% reduction in ER+ cancers, but an 11% increase in ER lesions in the treated group [1,2].

Bone mineral density is a sunogate of oestrogen exposure: those with the highest density have significantly increased free oestradiol [3]. Additionally there is a 2–3-fold increase in breast cancer risk among those in the highest quartile of bone density. Wolfe [10] developed a grading system for mammograms based on optical density and showed an increased risk in those with the densest (DY) breasts. A quality assurance review confirmed an association between rigour of methodology and relative risk of breast cancer in those with DY grades.

Other observations confirm the likely link between mammographic density and risk. In women taking hormone replacement therapy (HRT), there is a significant reduction in the sensitivity of mammography: for those in the 60–69 years age group this fell from 85% in non-users to 65% in those taking HRT. Cessation of HRT for as little as 10–30 days can lead to resolution of mammographic opacities or asymmetry. In a Canadian trial, 817 women with mammographic densities received either non-specific dietary advice or instructions on reducing dietary fat intake to 15% of their calories. After 2 years, those in the intervention group had significantly less dense breasts on digitised mammograms and this effect was seen even after controlling for weight loss. There was a significant reduction in plasma oestradiol and progesterone in the intervention group but this alone did not explain the change in mammographic density.

Oestrogens may also impact on the behaviour of the established disease. In 1991, the Guy's group showed that timing of surgery within the menstrual cycle had a significant effect on prognosis: for node-positive patients, the 10-year survival for those who had surgery in the luteal phase was 78% compared with 33% for those operated upon during the follicular phase [4]. Subsequent work confirmed the effect in a second dataset and also showed that subdivision of patients based on plasma progesterone levels at the time of surgery yielded two groups with differing prognoses [5]. For those with progesterone levels $\leqslant 4$ ng/ml, the 10-year survival was 54% whereas for those with levels > 4 ng/ml the 10-year survival was 84%.

Women having follicular phase surgery were more likely to have vascular invasion around tumours [6]. Additionally, 45% of postmenopausal women in the highest weight quartile had vascular invasion compared with 11% in the lowest quartile [7]. Tumour proliferation, measured by MIB1 staining, was examined in relation to the timing of surgery: the best outcome occurred in those with slow-growing tumours undergoing luteal phase surgery [8]. For women with ER+ tumours, there was a significant benefit from luteal phase surgery, but there was no difference in outcome for those with ER- tumours irrespective of the menstrual phase at the time of tumour excision [9].

In 1991, a collective decision was made to schedule all tumorectomies in premenopausal women with suspected breast cancer to the luteal phase. The outcome of two cohorts of women treated between 1986–1990 and 1991–1995 has been compared and the latter had a significantly better relapse-free survival. Timing of surgery

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was an independent prognositic variable in a multivariate analysis. This adds further evidence to support the hypothesis that endogenous oestrogens play not only an important aetiological role, but may also affect the prognosis in both pre- and postmenopausal women with early breast cancer.

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