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The origin of postmenopausal oestrogens

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Indirect evidence from past epidemiological and animal studies provide strong data for a causal relationship between postmenopausal oestrogen levels and the risk of breast cancer. Elderly women, for example, with a high bone mineral density (BMD) have an increased risk of breast cancer, especially advanced cancer, compared with women with low BMD [1]. Relationships between sex steroid hormone levels in plasma and the risk of breast cancer in postmenopausal women by use of a case–control study nested within the Nurses' Health Study has recently been published [2]. Among postmenopausal women not using hormone replacement therapy (HRT) at blood collection ($n = 11\,169$ women), 156 women were diagnosed with breast cancer after blood collection. Two control subjects were selected per case subject and matched with respect to age, menopausal status, month and time of day of blood collection, and fasting status at the time of blood collection. From comparisons of the highest and lowest quartiles, there was statistically significant positive association with the risk of breast cancer for circulating levels of oestradiol, oestrone, oestrone sulphate and dehydroepiandrosterone sulphate [2]. Recent results also indicate that the risk of endometrial cancer increases with increasing postmenopausal oestrogen levels as determined by the body mass index [3].

Oestrogens are derived from subsequent chemical reactions in which cholesterol (C27 sterol) is first converted to progestins (C21 steroid), then to androgens (C19 steroid) and finally aromatised to oestrogens (C18 steroid). In postmenopausal women, the most abundant circulating oestrogens are oestrone sulphate, and to a lesser extent oestradiol, both derived from the extragonadal aromatisation of androstenedione and testosterone. Androstenedione is produced by the adrenal cortex and testosterone is principally formed in peripheral tissues as a metabolic product of adrenal precursors [4]. The postmenopausal ovary is not a major androgen-producing gland [5].

Aromatase, the key enzyme for oestrogen biosynthesis—encoded by a single copy of the *CYP19* gene and regulated by tissue-specific promoter sites—converts androstenedione to oestrone and testosterone to oestradiol. Aromatase is present in a number of human tissues and cells such as adipose and skin fibroblasts, bone and brain. Aromatase increases with body weight; both El and E2 are correlated with body mass index [6]. Oestrogen-dependent tissues, whether pathological or not, can upregulate aromatase via the inappropriate activation of its promotors thereby generating high levels of intratissue E2, without significantly affecting circulating levels [7]. The new generation of aromatase inhibitors induce a $>70\%$ decrease in plasma and tissue oestrogens [8–10]. In the same tissues, other enzymes can lead to the local production of active oestrogens like oestrone sulphatase and 17β-hydroxysteroid dehydrogenase (HSD). Recent results demonstrate the important role of 17β-HSD in the increased conversion from El to E2 to maintain high intratumoral E2 levels in postmenopausal patients [11]. Because adrenal precursors decrease with age and oestrogen levels remain relatively constant throughout the menopause, other precursors may exist.

Free oestradiol, and not the sex hormone binding globulin (SHBG)- or albumin-bound fraction, is available biologically for action. Significant independent correlates of SHBG concentration are fat mass, physical activity, alcohol intake, serum oestradiol and insulin-like growth factor-l, all having a negative impact on SHBG and thereby increasing the levels of free oestrogens [12].

Some women may be more susceptible to oestrogens or HRT, such as those with a polymorphism in the *CYP 17* gene, another cytochrome P450 enzyme that is responsible for oestrogen biosynthesis [13]. Postmenopausal

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women with the A2 or C-allele have increased oestrogen levels [14]. Although the functional relevance of this is still unproven, such gene polymorphisms (others like *CYP1A1*, *COMT*, *CYP19*, are also being explored) may play a role in the link between environmental oestrogens and the interindividual risk of breast and endometrial cancer [15].

Various environmental contaminants, referred to as 'endocrine disrupters', may have a potential stimulatory effect on the Oestrogen Receptor (ER). Dichlorodiphenyltrichloroethane (DDT) has a strong chemical similarity to diethylstilbestrol (DES). Xeno-oestrogens, like the environmental oestrogen, bisphenol A, are also potent agonists in stimulating ER transcriptional activity [16]. Steroidal supplements of oestrogens and androgens like dehydroepiandrosterone (DHEA) may indirectly increase biologically available oestrogen levels and promote oestrogen-dependent tissue growth.

There is direct and indirect evidence on the effect of smoking on oestrogen levels. Smokers have an earlier menopause and smoking increases the levels of SHBG; geometric mean urinary excretion rates for oestradiol are significantly lower in a group of postmenopausal smokers compared with non-smokers [17].

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