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Oestrogen and female cancers: the past 100 years

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At the end of 1999, it is generally accepted that oestrogens increase the mitotic activity in breast and endometrial tissue and that errors in mechanics of cell division lead to malignancy. The importance of oophorectomy for breast cancer therapy was first shown by Beatson in 1896 [1]. Long before any link was made between the ovarian hormonal production and breast cancer, Beatson considered the effect of oophorectomy on lactation in cows after calving to keep up milk supply — a continuous process of fatty degeneration of proliferated ductal breast cells — as a potential treatment of cancer. To arrest cell proliferation and induce fatty degeneration in breast cancer tissue, he performed a bilateral oophorectomy on a premenopausal patient with relapsed inoperable breast cancer in a mastectomy scar. Eight months later, all cancer tissue had disappeared.

Ovarian transplantation studies in 1900 showed the ovary to be responsible for endometrial growth [2] and breast cancer development [3]. 'Ovarian therapy by ovarian extracts' was available for many years when Allen [4] localised and purified oestrogens in follicular fluid. Following this discovery, many compounds possessing oestrogenic properties were synthesised in the early 1930s. The synthetic non-steroidal compound stilboestrol, for many decades popular for pregnancy support and menopausal health, was synthesised in 1938. Greene in 1941 [5] used stilboestrol to induce endometrial adenocarcinomas in rabbits, as did Meissner in 1957 [6]. Geist in 1941 [7] warned of endometrial abnormalities developing in women on synthetic oestrogens but it was Gusberg in 1947 [8] and Jensen in 1954 [9] who published how long-term exogenous oestrogens for menopausal health increased a woman's endometrial cancer risk. However, pure oestrogens in non-hysterectomised women were extensively used until 1975 [10,11] when they were associated with a 14.0 relative risk (RR) for endometrial cancer. The anti-oestrogenic potential of progesterone on the human endometrium was already described in 1961 by Kelly and Baker [12]. Dockerty in 1951 [13] reported on endogenous oestrogens from ovarian tumours accompanying endometrial adenocarcinoma. That endogenous oestrogens are a risk factor for both breast and endometrial cancers was shown by similar age-specific incidence curves in 1955 [14].

MacDonald in 1969 [15] demonstrated the origin of endogenous postmenopausal oestrogens from aromatisation of androstenedione to oestrone in peripheral adipose tissue. The conversion rate to oestrone correlated with the quantity of body fat; obesity became an important risk factor for oestrogen-related cancers [16]. The process of aromatisation is also increased inside malignant breast tissues [17] leading to increased oestradiol levels in the breast cancer cell and its environment. That serum oestrogen levels are an important risk factor for postmenopausal female cancers was shown by Toniolo in 1995 [18] and by others. Overall, women who were diagnosed with breast cancer had a 15% (statistically significant) higher mean serum concentration of oestradiol than the control women in at least six studies.

Jensen in 1958 [19] opened a new era of female hormone research by showing the mechanisms for oestradiol and progesterone incorporation into specific cytoplasmic protein receptors and subsequent transport into the nucleus to effect translation and transcription for ultimate hormonal alterations in target cells. The discovery of the first oestrogen receptor, further described by Toft and Gorski [20], as a marker for response to hormones and anti-hormones such as tamoxifen in the late 1960s revolutionised hormonal therapy for hormone-dependent cancers. Before the tamoxifen era, from the 1940s until 1970, available hormonal therapies for gynaecological cancers included pharmacological doses of synthetic oestrogens, androgens, corticosteroids or progestins obtaining similar results as with oophorectomy, ovarian irradiation, hypophysectomy and adrenalectomy.

Although tamoxifen has few toxic side-effects and is very efficacious in all stages of breast cancer, its endometrial side-effects pushed the industry to develop new compounds. In the early 1980s, molecules that inhibit

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oestrogen formation in pre- and postmenopausal patients like luteinising hormone-releasing hormone (LH-RH) agonists and aromatase inhibitors, respectively, became available for the treatment of advanced breast and endometrial cancers. The first generation of aromatase inhibitors were not specific and, therefore, toxic. Today, a number of potent and very selective aromatase inhibitors are available. There is renewed interest in anti-oestrogens, now called selective oestrogen receptor modulators (SERMs), without uterine side-effects, being anti-oestrogenic in the breast but oestrogenic in the bone and cardiovascular system. New hormonal developments for after 2000 are pure anti-oestrogens, antiprogestins, somatostatin analogues and LH-RH antagonists.

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Molecular mechanisms of oestrogen — the gynaecologists' viewpoint

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The use of oestrogen as a hormone replacement therapy (HRT) for postmenopausal women is increasing. There are known benefits of relief of climacteric-related mood and vasomotor symptoms and there is protection against osteoporosis and cardiovascular disease. The applications of oestrogen are limited by the need for a progestagen in non-hysterectomised women, and by women's dislike of uterine bleeding, and fear of breast cancer. Molecular biology perhaps holds the key for widening the clinical use of HRT. By studying the molecular actions of oestrogen, compounds are being developed that will mimic its action while avoiding the unwanted effects associated with conventional therapy.

Nuclear hormone receptors are transcription factors that can initiate or amplify the transcription of genes that are hormonally responsive. The oestrogen receptor (ER) protein consists of 595 amino acids, and is separated into six functional domains. Each domain is responsible for different functions: binding hormones, binding hormone response elements, or containing transcription activation functions, to initiate gene transcription.

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