Hormonal therapy for cancer

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Abstract

Hormone therapy is an effective and non-toxic therapy for oestrogen and progesterone receptor-positive breast cancer and prostate cancer. Serum levels of oestradiol and testosterone are controlled by the hypothalamic–pituitary–gonadal pathway. Oestradiol is produced in premenopausal women from the ovaries and in postmenopausal women by peripheral conversion of adrenal androgens by aromatase. In premenopausal women with breast cancer and men with prostate cancer, treatment is primarily achieved by castration. In postmenopausal women selective oestrogen receptor modulators (e.g. tamoxifen) or aromatase inhibitors are used. Hormone therapy can be used to reduce the size of the primary cancer prior to radical surgery or radiotherapy or to reduce the risk of recurrence. Hormone therapy is highly effective in patients with locally advanced or metastatic disease, with a high response rate. Most patients eventually relapse with 'castrate-refractory' disease, for which increasing numbers of active agents are entering clinical practice.

Keywords Androgen deprivation therapy; anti-androgens; aromatase inhibitors; breast cancer; hormone therapy; prostate cancer; selective oestrogen receptor modulators

Aetiology (see also *Breast Cancer* on pages 42–46 and *Prostate Cancer* on pages 47–51 of this issue)

This paper will concentrate on the management of breast and prostate cancers in which the impact of hormone therapy is most clinically significant. Increased exposure to endogenous or exogenous oestrogens may be linked to the development of breast cancer (Table 1). However, there is no evidence that exposure to androgens is important in the development of prostate cancer.

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What's new?

- The mechanisms behind resistance to hormonal therapies are being better characterized
- New drugs targeting these mechanisms have shown a survival advantage over previous best care and have entered routine practice
- Further agents overcoming resistance to these newer agents are now being studied
- In breast cancer, pathway inhibitors are used in combination with aromatase inhibitors to overcome resistance
- In prostate cancer these are abiraterone acetate and enzalutamide

Historical evidence

In 1896 Beatson demonstrated that surgical oophorectomy resulted in tumour regression in premenopausal women with metastatic breast cancer. Charles Huggins was awarded the Nobel Prize for medicine in 1966 following his discovery that surgical orchidectomy was a successful treatment for metastatic prostate cancer.

Hormone synthesis

Oestrogen is synthesized from cholesterol in the parafollicular ovaries in premenopausal women via the hypothalamic–pituitary–gonadal axis (Figure 1), and in the adrenals in postmenopausal women. In premenopausal women, oestrogen production is cyclical: gonadotrophin-releasing hormone (GnRH) is released from the hypothalamus with a circadian rhythm under direct feedback by circulating hormones. GnRH reacts with anterior pituitary receptors, leading to the release of luteinizing and follicle-stimulating hormone; these stimulate the ovaries to produce oestradiol.

In postmenopausal women, the main site of oestrogen synthesis is adipose tissue. Here, adrenal androgens (e.g. androstenedione) are converted by aromatase to oestrone. Oestrone is then converted to oestradiol by 17β-OH dehydrogenase. Postmenopausal synthesis varies depending on environmental and genetic factors (e.g. obesity).

In men, the main circulating androgen is testosterone, 90% of which is produced by the testicular Leydig cells under control of the hypothalamic–pituitary axis, as above. The remaining circulating androgens (e.g. dihydroxyandrostenedione) are

Hormonal risks for breast cancer

Risk factors	Protective factors
Early menarche	Breast-feeding
Late menopause	Young age at full-term pregnancy
Nulliparity	
Obesity	
Hormone replacement therapy	

Table 1

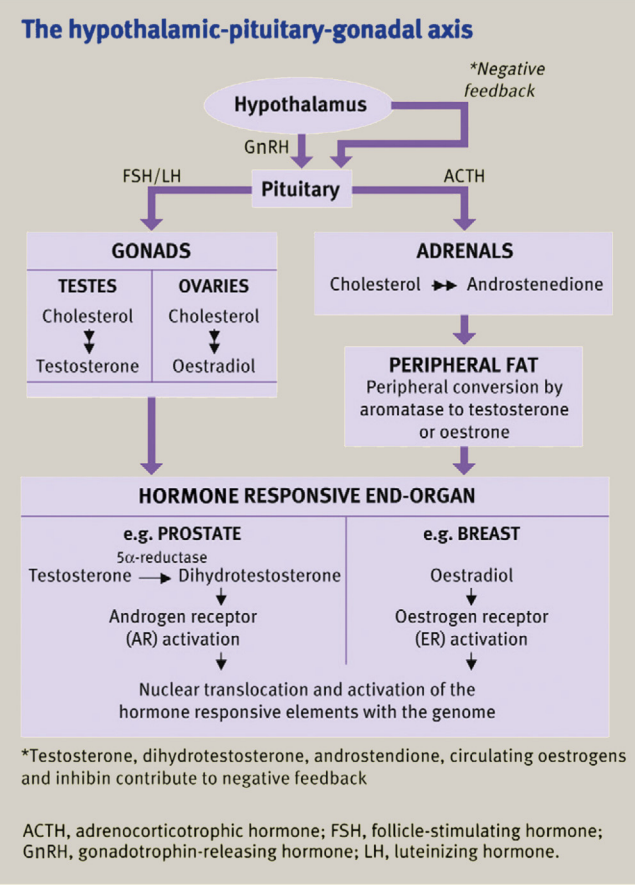

Figure 1

produced in the adrenal cortex from cholesterol. Testosterone is metabolized by 5α-reductase within the prostate to the more biologically active dihydrotestosterone, which acts as the ligand for the androgen receptor (AR).

Hormone receptors

In breast cancer, approximately 80% of postmenopausal women and 50% of premenopausal women have hormone receptor-positive disease. The degree of positivity is defined by the level of expression of both oestrogen (ER) and progesterone receptors, which are routinely measured immunohistochemically in newly diagnosed cases. Systemic treatment and, to some extent, prognosis is guided by hormone receptor status.

In contrast, measurement of ARs is not currently routinely performed in prostate cancer — it has no therapeutic or prognostic value because both hormone-dependent and 'castrate-refractory' prostate cancers (CRPCs) possess functioning ARs. Recent work suggests that AR variants may underlie resistance to castration.[1]

Hormone therapy in breast cancer

Ovarian ablation

In premenopausal women oestrogen suppression is achieved by chemical ablation, radiation to the ovaries or surgical oophorectomy. Chemical ablation is reversible and achieved by using a GnRH agonist (GnRHa) such as goserelin, usually as a monthly depot injection.

Other hormonal agents in breast cancer

An increasing number of hormonal treatment options are available to treat breast cancer. A description of the different licensed drugs is given in Table 2. The most commonly used treatments include tamoxifen and aromatase inhibitors (AIs).

Tamoxifen: this is a selective oestrogen receptor modulator with complex actions on ERs, acting predominantly as an antagonist, with a weak agonist effects. In ER-positive early breast cancer, 5 years of tamoxifen after surgery reduces the annual recurrence rate by 41% and annual mortality rate by 34%.[2] There is evidence of a reduction in breast cancer recurrence and mortality by continuing tamoxifen in ER-positive disease for 10 years rather than stopping at 5 years.[3]

Tamoxifen may be used in premenopausal and postmenopausal women. The main adverse effects are hot flushes, night sweats and vaginal discharge. There is an increased risk of thrombotic events. Vaginal bleeding should be promptly evaluated because of the increased risk of endometrial cancer.[4]

Aromatase inhibitors: several Phase III clinical trials have established third-generation AIs as the new gold standard in the adjuvant hormonal treatment of receptor-positive early breast cancer. They are contraindicated in premenopausal women

Hormonal therapies in breast cancer

Drug	Type	Dose/route	Mode of action
Tamoxifen	Anti-oestrogen	20 mg daily p.o.	Competes with oestradiol for ER binding
Anastrozole	Non-steroidal aromatase inhibitor	1 mg daily p.o.	Competitive aromatase inhibition
Letrozole	Non-steroidal aromatase inhibitor	2.5 mg daily p.o.	Competitive aromatase inhibition
Exemestane	Steroidal aromatase inhibitor	25 mg daily p.o.	Irreversible aromatase inhibition
Fulvestrant	Oestrogen receptor antagonist	250 mg monthly i.m.	Down-regulation of the ER protein
Megestrol acetate	Progestin	80—160 mg daily p.o.	Cellular action not fully understood Down-regulation of ovarian steroidogenesis

ER, oestrogen receptor; i.m., intramuscular; p.o., oral.

Table 2