Oestrogen and breast cancer: results from the WHI trial

In *The Lancet Oncology*, the Women’s Health Initiative (WHI) investigators report that receipt of conjugated equine oestrogen for a median of 5.9 years reduced the risk of invasive breast cancer by 23% compared with placebo (151 cases in 5310 women who received oestrogen vs 199 cases in 5429 controls; p=0.02). Women who did develop breast cancer after receipt of oestrogen had significantly reduced breast cancer-specific mortality (six deaths in the oestrogen group vs 16 deaths in controls; p=0.03) and all-cause mortality (30 deaths vs 50 deaths; p=0.04). This preventive effect occurred at all ages and continued beyond the period of oestrogen use, a carryover effect also noted in prevention trials of tamoxifen.\(^1\)

Although modest, the WHI results are significant and raise important questions about their disparity with many observational studies and the mechanism of reported benefit with oestrogen therapy. Most observational studies on the use of oestrogen-only hormone replacement suggest an increased risk of breast cancer, whereas some show risk neutrality, and a few agree with the reduced risk reported by the WHI.\(^2\) Traditionally, randomised controlled trials have greater validity than do observational studies. However, the overall weight of evidence in terms of number of independent studies is also important, and the WHI trial is the only randomised controlled trial examining oestrogen therapy that supports this view. Large databases in observational studies reduce random error, but no amount of observational data can overcome potential biases in study design. This feature is especially relevant when the exposure is related to lifestyle or involves personal choice such as attendance to screening mammography.

Oestrogens stimulate development and growth of breast cancer, so how can their beneficial effect in the WHI trial be explained? One possibility is the propensity for breast tumour cells to adapt to grow best at the prevailing oestrogen concentration, in line with shifts in the oestrogen dose–response curve as shown by Song and colleagues.\(^4\) When oestrogen concentrations were reduced in a medium of MCF-7 breast tumour cells, the cells stopped growing, but after 3 months they adapted to grow best at the reduced concentration and growth was inhibited when increased concentrations of oestrogen were added. This finding helps explain the mechanism of response to high-dose oestrogens in advanced breast cancer that has been noted clinically for 70 years.\(^5\) Thus, when oestrogen concentrations decline after the menopause any tumours present in the breast might adapt and grow at the lower concentration but then are potentially inhibited by higher concentrations provided as replacement therapy. For patients with advanced breast cancer who respond and then progress on high-dose oestrogen, stopping of treatment could result in a response (withdrawal response), suggesting that the tumour had adapted to grow at the higher dose. Withdrawal responses might explain the improved prognosis of women who developed breast cancer while receiving oestrogen therapy. Withdrawal responses related to cessation of such therapy have been reported and result in extended remission.\(^6\) An alternative explanation is that oestrogen provided as therapy has an anti-oestrogenic activity. Conjugated equine oestrogens are derived from the urine of pregnant mares and are made up of more than ten different oestrogens.\(^7\) Some of these oestrogens might be anti-oestrogenic and bind to the inhibitory oestrogen receptor β to a greater extent than does 17β-oestradiol.

The present results of WHI\(^8\) should be seen in the context of the update of the study in 2011 reporting the effects of oestrogen on overall health.\(^8\) No overall difference was noted in participants’ global index of health (including cardiovascular disease, thrombosis and embolism, breast and colorectal cancer, hip fracture, and death from all causes). However this null result masks an unexpected but significant interaction with age (p=0.009) with health improvements in young women and health decrements in older women. Young women (50–59 years) taking oestrogen were significantly less likely to have coronary heart disease, myocardial infarction, and death from all causes, not only with respect to older women but also placebo controls of the same age. The reasons for such an interaction with age deserve further investigation.

Whether the benefits of oestrogen therapy in young women can be translated to all oestrogen-only hormone replacement therapy is unknown, and perhaps only conjugated equine oestrogens should be prescribed at present. The Kronos Early Estrogen Prevention Study (KEEPS) trial\(^9\) is comparing the cardiovascular effect of conjugated equine oestrogens and transdermal
Screening for anal cancer: endpoints needed

Anal cancer is very rare in the general population, but much more common in well defined, high-risk populations, including women with a previous cervical precancer, men who have sex with men (MSM), and individuals with HIV.

Infection with carcinogenic human papillomavirus (HPV) has been increasingly recognised to cause anal cancer. In *The Lancet Oncology*, Dorothy Machalek and colleagues report their findings from a systematic review and meta-analysis of anal HPV infection and associated lesions in MSM, underscoring the disease burden in HIV-positive MSM.1 They recorded a prevalence of high-risk anal HPV in HIV-positive MSM of 73·5% (95% CI 63·9–83·0). In the same population, the prevalence of high-grade anal intraepithelial neoplasia (AIN) was 29·1% (22·8–35·4) and the estimated annual cancer incidence was 45·9 per 100 000 HIV-positive MSM (95% CI 31·2–60·3).1

Secondary prevention of cervical cancer by screening for and treatment of precancers has been very successful.1 Several key factors have made this success possible: sufficiently high prevalence of precancers, the ability to directly sample the tissue at risk, diagnostic markers that provide sufficiently reliable risk estimates, and an intervention that removes the tissue at risk, effectively interrupting natural history without causing major harm. Although screening to prevent cervical cancer was introduced without full understanding of its natural history, research during the past 30 years has led to the development of a progression model that explains the relevant steps from HPV infection to cervical cancer (figure).

With the high level of understanding about HPV-related carcinogenesis and experience from cervical cancer screening, efforts to address screening for anal cancer should have a head start. HIV-positive MSM are a well-defined population—they are often followed up closely at specialised clinics to monitor antiretroviral therapy and for surveillance of AIDS-related disease. Machalek and colleagues report a high disease burden in HIV-positive men who have sex with men.