

Editorial

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## Double-faced Estrogen

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A wealth of evidence indicates that steroid hormone estrogens contribute to the tumorigenesis of many cancer types [1-5]. They can promote cell proliferation and stimulate cell division, while also cause random errors during DNA replication [6-10].

However, back in 1940s, the first chemotherapy agent for breast cancer was high dose of synthetic estrogen DES (diethylstilbestrol) [11]. DES was also used to treat metastatic prostate cancer. Exact mechanism of the cancer suppressive effect of estrogens is not known, but about 30% patients responded to the treatment. In 1970s, tamoxifen was developed [12]. After the publication of the landmark study by Mayo Clinic comparing the effect of tamoxifen with DES showing that far fewer adverse effect was seen in tamoxifen-treated group [13], tamoxifen became the “gold standard” for treating ER-positive breast cancer. The practice of using DES to treat prostate cancer was also mostly replaced with the introduction of leuprolide in 1985. The fact that estrogens have been used therapeutically to treat cancer is unknown to most clinicians trained in the era of tamoxifen and other anti-estrogen drugs.

Interestingly, several recent studies now signal a potential comeback of estrogens as cancer treatment or prevention agents. The long-term follow-up of the Mayo Clinic study showed significantly improved survival with patients treated with DES [14]. In addition, the analysis of estrogen replacement therapy in the Women's Health Initiative (WHI) double-blind, placebo-controlled randomized trial in 10,739 postmenopausal women showed a decrease risk for invasive breast cancer [15]. The authors concluded that exogenous estrogens are protective, but endogenous estrogens are carcinogenic (Cancer Res 2009;69(24 Suppl):Abstract nr 908). In 2001, the clinical benefit of using high dose DES treating metastatic breast cancer which are resistant to anti-hormone therapies. Complete or partial response was seen in one-third of the patients.

Where does the anti-tumor effect of estrogens come from? Studies have shown that high concentration estrogens can induce apoptosis through FAS/FASL pathway [16]. Ellis et al. [17] found that 6mg daily dose of estrogen is as effective as 30 mg daily on metastatic cancer and the low dose had fewer side effects. The idea is that cells survive the long-term estrogen deprivation become sensitive to re-exposure of estrogen even at physiological dose [18].

The estrogens can undergo extensive oxidative metabolism, which produce mostly 2-hydroxyestrone/estradiol, and 4-hydroxyestrone/estradiol. Catecholestrogens have been reported as potential carcinogens and induce DNA mutations by evidence of loss of heterozygosity in cultured cells [19]. However, 2-hydroxyestradiol seems to be less of a carcinogen since 500-fold more concentrated 2-hydroxyestradiol is needed to trigger DNA mutation than 4-hydroxyestradiol or estradiol itself. The catecholestrogens can be further metabolized by catechol-O-methyltransferase (COMT) into methoxyestrogens [20]. Methoxyestrogens, especially 2-methoxyestrogens have potent tumor-suppressive effects both *in vitro* [21-23], and *in vivo*. 2-methoxyestrogens have been reported to disrupt microtubule dynamics by destabilizing the tubulin polymers [23]. Several phase II clinical trials have been completed with 2ME2 showing some promise in suppressive several types of cancer. Whether some of the anti-tumor effect is mediated by estrogen metabolites is interesting, yet unexplored.

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