The WHO classified estrogens as carcinogenic. Within the complex metabolism of estrogens genotoxic and protective metabolites can be produced. Certain metabolites act mainly as growth factors, others can cause apoptosis or capture toxic radicals. However, additional oxidative cell-stress makes possible a 'radicalic one electron oxidation', stabilizing semiquinon-quinon complexes, which can react with DNA even at very low concentrations causing mutations. However, proliferation to the clinical cancer during treatment with E2-only is slow, and protective mechanisms can work, can even destroy proliferating cancer cells before producing clinical cancer. This can explain results in the WHI-study, estrogen-only significantly decreasing the breast cancer risk. But with certain progestogens or other promoting factors like stromal growth factors the protection may not have time to work. We could demonstrate that the estradiol metabolism can be influenced by administration route and the type of progestin. In addition we found, that life-style factors such as physical activity and smoking as well as genetic polymorphisms of key enzymes involved in the metabolism may have a crucial impact. In the presence of those factors transdermal estrogen should be recommended to minimize the production of possible toxic metabolites, and further research should identify possible screening for women at increased risk.