Recent studies have shown estradiol (E2) in combination with natural progesterone (P) to induce different gene expression than in combination with synthetic progestogens, in breast cells in vitro and in vivo. 77 healthy women were randomized to sequential hormone therapy with two 28 day cycles of either oral 0.625 mg Conjugated Equine Estrogens (CEE) or 2.5g 0.06% (1.5 mg E2) percutaneous E2- gel daily, with the addition of respectively 5 mg of oral Medroxyprogesterone acetate (MPA), or 200 mg of oral micronized P, daily, for the last 14/28 days per cycle. Microarray analysis was assessed on Core needle biopsies from 8 patients before and after 2 months of treatment. According to IPA analysis, 225 genes were found to be involved in mammary tumor development, 198 genes for CEE/MPA and 34 for E2P. Out of these: IPA database found 14 genes to be regulated to increase mammary tumor significantly more for CEE/MPA than for E2/P v.s. 4 genes more for E2/P than CEE/MPA. In 30 patients, 15 in each treatment group with sufficient mRNA, RT-PCR was performed from the biopsies before and after 2 months of treatment to assess the activity of the above genes. In total, the change in expression of 16 genes was measured. Results: PCR analysis showed a significant increase in MKi-67 gene expression (p<0.05) in the CEE/MPA but not the E2P group. For this group, the Prolactin gene was down-regulated (p < 0.05) as well as the Bcl-2 gene at borderline significance (p=0.0535). For CEE/MPA but not for E2/P, there was a positive correlation between IGF1 gene expression and Ki-67 MIB1 protein during treatment. as well as marked activation of the PGR B gene in cases with high % pos Ki-67 MIB1 cells, where there was a tendency for down-regulation of protective genes as Cav -1 and FBX-4. Conclusion: The PCR analysis confirms earlier micro-array data of a significant increase in MKi-67 gene expression (p<0.05) in the CEE/MPA but not the E2P group. In combination with the reduction in the anti-apoptotic Bcl-2 gene and proliferative Prolactin genes in the E2/P group this, adds to data showing that treatment with percutaneous E2 in combination with oral micronized P induces less proliferation and less adverse expression of some important genes regulating proliferation and apoptosis in vivo.