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Choice of progestogen for HRT in menopausal women

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The WHI has been the only large double-blind placebo-controlled study testing the risk of breast cancer (BC) using HRT. No increased risk using estrogen (E)-only was seen, even a significant decrease of mortality which persisted even during the recent 18-year Follow-up of the study (HR 0.55, 0.33-0.92; Manson et al. 2017). In contrast in the combined arm the risk increased. For total evidence also observational studies should be considered. In about 20 studies using mostly MPA or NETA an increased risk has been observed comparable with the WHI. Only for progesterone and dydrogesterone (retro-isomer of progesterone) comparing directly with other progestogens no increased risk has been seen up to 5-8 years, but longer treatment also increased the risk. In contrast the mortality due to BC after use of E-only and combined HRT decreased to about 30% in a dozen observational studies independent from the type and regimen of HRT, recently confirmed in a Finnish study evaluating 490,000 women using estradiol (E2) plus different progestogens (Mikkola et al. 2016). Experimental research can explain those results: Various carcinoprotective effects can work, even by E2 itself like apoptosis and production of carcinoprotective E2-metabolites. If in a population for more women the proliferation of BC cells is slow enough to destroy the cancer before its clinical detection, the statistics overall will show a decrease of risk. However, if fast proliferation, clinical cancer can develop. Progestogens can accelerate proliferation via special cell-membrane components which we detected in patients with BC, and we found differences comparing all available progestogens. In addition also other carcinoprotective mechanisms may work like carcinoprotective E2-metabolites or special protective enzyme activities. Derived from those mechanism future research may provide screening for patients at risk. For clinical practice this may be more useful than performing more studies because (derived from already existing more than 70 studies) the overall risk is small and the solution of the problem could be to detect those few patients who are at risk by evaluating risk factors and mechanisms for BC development.

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