

BREAST CANCER AND HORMONES: FACT OR FICTION

A.O.Mueck

University Women's Hospital of Tuebingen, Dept. of Endocrinology and Centre of Women's Health, D-72076 Tuebingen, Germany

The question of increased breast cancer risk caused by sexual steroids like oral contraceptives (OC) or hormone replacement therapy has been controversially discussed since 30 years. An update of epidemiological data on breast cancer risk and OC will be given during this congress by David Cibula (Prague). Based on epidemiological data, most studies did not show an increased risk during OC, but there are also studies which did.

Regarding the biological plausibility it is well known that estrogens can act as growth factor in promoting the proliferation of breast cancer cells, and we recently were able to demonstrate this effect also for ethinylestradiol (EE), the estrogenic component in OC. However, in addition there is another important mechanism, not only proliferating but also causing cancer during treatment with estrogens. There is evidence in vitro, in animal experiments and also in human beings that certain estrogen metabolites may trigger the initiation of mutations. According to own, already extensively published experiments, there is evidence that estrogen metabolites are not only inactive waste products, but have own biological properties even at very low concentrations which can exceed manifold those of their parent substance. We also could demonstrate that for both pathways of the different mechanisms the addition of a progestogen may further increase the risk by 1) increasing the proliferation mechanism, especially via effects with stromal growth factors (which even can have a much more proliferative potency compared to estrogens) and/or 2) by influencing the pattern of estrogen metabolism into the direction of increased production of potential genotoxic metabolites.

Following this biological evidence the World Health Organization (WHO) classified estrogens as well as estrogen/progestogen combinations as 'carcinogenic in humans' (*Lancet Oncology 2005; 6: 552-553*). Nevertheless, there still remains the question why epidemiological data are controversial, and indeed mostly do not suggest an increased risk of breast cancer. It seems that the risk is very small, but this does not exclude that a certain small subgroup of women may be on increased risk, even on high risk – after all, the most important question seems to be, if we could be able to screen for those women.

To answer this question most research had focused on the first mechanism – increase of breast epithelial cell proliferation by estrogenic impact. Although this mechanism also might lead to mutations due to mistakes during DNA-replication it appears to be not as important for causing cancer because a huge battery of repair mechanisms can work and also avoid further mistakes. All in all we already have good knowledge regarding this pathway of potential development of breast cancer, but research concluded much more on potential therapy of existing breast cancer and not if and how to screen risk patients according to this pathway of carcinogenesis, summarized as follows:

The actions of estrogens are mediated via two different receptor subtypes, i.e. ER-alpha and ER-beta. Ligand-bound ERs can work in the classical genomic pathway which includes binding to the DNA estrogen responsive element and activation of the transcription machinery. The non-genomic pathway includes cross-reactions of the ER with intracellular signal molecules such as the tyrosine kinase domain of growth factor receptors or directly with the mitogenic kinase PI3K. In addition the ER-complex can bind to DNA elements such as AP1 or cyclin D1.

Future research must concentrate also on the second mechanism because certain estrogen metabolites have direct carcinogenic potency by oxidative processes leading to DNA strand breaks and inducing mutations. We already know that life-style factors such as physical activity as well as genetic polymorphisms of the enzymes involved in the formation and degradation of the catechol estrogens can influence the metabolic pattern. Thus, it should be able, to screen for patients of increased risk regarding this pathway, and even more, there is biochemical evidence, that the whole detrimental pathway may not work, if excessive oxidative cell stress like smoking is avoided or, may be in future, also antioxidative strategies are applied.

Via this pathway especially the 4-quinones produced from 4-catechol-estrogens are supposed to play an important role. However, their toxic effects need special oxidative cell stress to manage a crucial one-electron oxidation from semiquinones to quinones, which can be prevented by various cellular defence mechanisms. We have been able to assess the biological potency of various metabolites and to demonstrate that the pattern of estrogen metabolism during hormonal treatment can be influenced by administration route and the type of added progestogen.

Our present conclusion is that the clinical importance of potential genotoxic metabolites still awaits further research and there is no reason to change current clinical practice assessing benefits and risks during treatment with OC. However, according to the biological evidence we propose for practical management two, in our view, important conclusions:

1) Older women should have (and do have according to clinical data) a higher risk of breast cancer due to proliferation mechanisms of already preexisting cancer cells. To date we have no possibility to avoid this risk and we should inform the patients about a potential risk, which is according to clinical data about 1 per 1000 per year in perimenopausal women, i.e. very low. Like for all other older women, gynecological examinations should be made on a regular, at least yearly basis.

2) Very young women, may be below 14 to 16 years of age, could be especially of risk according to the second pathway, because they still have morphological vulnerable breast tissue structures, where protective effects destroying the genotoxic metabolites may not work. Environmental factors causing oxidative cell stress may increase this risk and factors like smoking should be avoided because it might not only trigger proliferation but can cause breast cancer. For future research it seems important to develop strategies to screen for those young patients on increased risk e.g. by assessing genetic polymorphisms and potential genotoxic metabolites.