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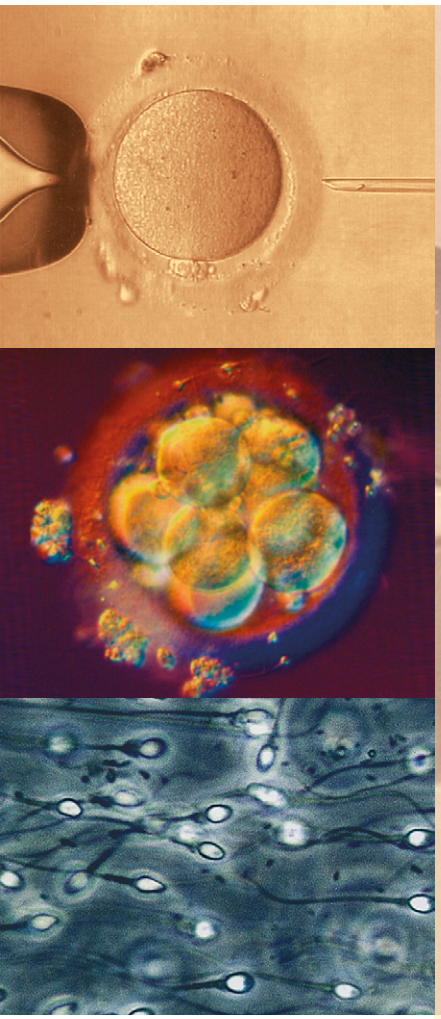

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Safety Issues in Hormonal Replacement Therapy

A. O. Mueck

Since the study Women's Health Initiative (WHI) has been stopped 2002 due to increased risk of venous thromboembolism, myocardial infarction, stroke and breast cancer, safety issues have got great concern especially in Hormone Replacement Therapy (HRT) in women, used for more than 40 years for treatment of climacteric and urogenital symptoms and/or to prevent osteoporotic fractures. However, using lower dosages, other hormonal components and/or transdermal instead of oral application can reduce those risks although not demonstrated in a placebo-controlled study comparable to WHI. However, this has been shown in large case/control- and cohort-studies reflecting more practical conditions in contrast to WHI, and also is plausible due to extensive experimental research. This even is true for breast cancer, main issue for women, although the WHO has stated "carcinogenicity" using estrogen/progestogens combinations. Own and other new results of intensive research suggest that there are differences in the risk dependent on the progestogen component regarding proliferation mechanisms, and with respect to the development of possible genotoxic estrogen metabolites additional factors including certain genetic polymorphisms are necessary for causal initiation of cancer. Regarding cardiovascular safety in most patients possible risks can be avoided by early start of adequate HRT, and for myocardial infarction as well as colon cancer, even prevention can be expected although these effects are no accepted indications to start hormonal therapy. **J Reproduktionsmed Endokrinol 2010; 7 (4): 220–4.**

Key words: hormone therapy, safety, WHI, transdermal HRT, cardiovascular risks, breast cancer, hormonal mechanisms

Introduction

Safety issues in hormonal therapy have been discussed in recent years especially in the field of hormone replacement therapy (HRT). The most important study "Women's Health Initiative" (WHI) has been stopped in 2002 due to increased risk of venous thromboembolism, myocardial infarction, stroke and breast cancer. This overview will concentrate on these main risks. There are options of different HRT regimens to minimize these risks. Especially plausible is the use of minimal dosages of transdermal administration avoiding first liver passage which should reduce hepatic and cardiovascular risks, which, however, is not based on placebo-controlled studies. For breast cancer development, first fear of most women, further research on the two main mechanisms are most important – proliferation effects and conditions for potential genotoxic estrogen metabolites. To individualize hormonal therapy also preexisting risks have to be considered, and with early start, within a "window of opportunity", most patients will benefit from HRT if indicated.

Controversies about the safety of different hormone therapies have been since many years particularly regarding the use of hormonal contraceptives and hormone replacement therapy (HRT). Whereas for contraceptives newer studies especially investigating the risk of breast cancer have been suggested only minimal risk [1, 2], if at all, the discussion on HRT reached a peak after the publication of the Women's Health Initiative (WHI) in 2003–2004 [3, 4]. Besides the already known risk of venous thromboembolism the WHI confirmed an increased risk of stroke and coronary heart disease although this was relevant only with start of HRT in women older than 60 years of age [5, 6].

WHI – Basis of Official Recommendations on HRT Use

The WHI is the only study on HRT with placebo-controlled design, clinical endpoints and high statistical power due to a large patient sample. WHI was performed in two separate trials, in non-hysterectomized women (n = 16.608) using conjugated equine estrogens (CEE) 0.625 mg/day continuously combined with medroxyprogesterone acetate (MPA) 2.5 mg/day (study 5 years) [3], and in hysterectomized women (n = 10.739) using CEE-only 0.625 mg/day (study 7 years) [4]. Although this study has been the basis of most official recommendations, like recently of the German guideline for the use of HRT [7], the WHI cannot reflect the practical conditions, because on average the women were too old at start with HRT (about 65 yrs), and the population was at high risk particularly for cardiovascular diseases: Table 1 summarizes the main risk factors.

For younger women (under 60 yrs) no increased arterial risks have been ob-

Table 1: WHI-study – A Population High of Cardiovascular Risks [3, 4].

	Estrogen only	Combined HRT
Mean age during the study (years)	67	66
BMI > 30 kg/m²	45 %	34 %
Smokers (before and/or during WHI)	48 %	50 %
Hypertension	48 %	36 %
Preexisting cardiovascular diseases*	ca. 10 %	ca. 10 %

* Patients after venous thromboembolism, pulmonary embolism, after myocardial infarction, stroke, angina pectoris, after bypass-surgery, angioplasty, preexisting diabetes mellitus, preexisting severe dyslipoproteinemia.

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served correlating with about 40 observational trials as well as with hundreds of experimental studies – there was even a tendency to cardiovascular protection [5, 6, 8]. However, these results have not been considered in most official guidelines, because the study was not powered enough for subgroup evaluations. Nevertheless, based on the whole evidence there is a "window of opportunity" with more benefit compared to risk if HRT is early started within 5–10 years after menopause. For cardiovascular safety issues this is one of the most important points regarding practical use.

In the WHI only one HRT preparation was tested, and only in one dose – both also not reflecting practical conditions. At least in Europe we use various forms of therapies regarding type of hormones, dosage and application form. Although placebo-controlled studies for those preparations are lacking, for safety issues the evidence of observational and experimental studies should be considered suggesting that the main risks observed in WHI can be reduced, especially by use of transdermal HRT.

Reduction of Cardiovascular Risks by Use of Transdermal HRT

Contrary to the USA, in Europe the non-oral administration of an estradiol replacement was available since the 1980s and recommended especially for women with preexisting cardiovascular risk. The first obvious advantage is avoidance of the first liver passage which with oral estrogens in many circumstances are unfavourable for menopausal women. These include increased triglycerides, linked to a decrease in the size of LDL particles, to a higher level of C-reactive protein and activation of coagulation [9–12]. This pharmacological, not "physiological" method of administration, on the one hand, reduces the anti-atherogenic effects of estradiol, and, on the other hand, can add venous and arterial thromboembolism risks.

As regards the main intermediate and well-known risk markers (triglycerides, size of LDL particles, coagulation, C-reactive-protein), randomised studies have consistently confirmed the superiority of transdermal estradiol replacement to oral formulations, which makes plausible a real difference in the benefit/risk ratio between the two routes of administration [9–16]. However, until now only few clinical endpoint studies have demonstrated this difference.

In a recent very large Danish study (n = 698 098; aged 51–69) 4.947 myocardial incidents have been identified [17]. Overall, there was no increase of risk (RR 1.03; 95 %-CI: 0.95–1.11), but subgroups with oral HRT were assessed to be at increased risk. In contrast, with transdermal estrogen (patch or gel) a significant decrease of risk of about 40 % was observed. No association were found with progestogen type or estrogen dose. Regarding the use in patients with angiographically proven ischemic heart disease only one small randomised study (PHASE) failed to demonstrate this potential safety improvement [18]. However, this study had important limitations including the small sample size (n = 255) and high dropout rate (40 % in the HRT arm).

Regarding the risk of venous thromboembolism it is well established that oral estrogen therapy activates blood coagulation [10, 13] and increases the risk of venous thromboembolism (VTE) in postmenopausal women [3, 4, 19] whereas transdermal estrogen has little or no effect on haemostasis [10, 13, 20]. Randomised trials have shown that oral estrogen increased plasma level of prothrombin fragment F1+2, which is a marker for in vivo thrombin generation and a predictor of VTE risk [20, 21], and APC resistance has been demonstrated using oral ET (22), which did not apply to transdermal application [23].

However, clinical data have been scarce although recent observational studies suggest that – compared with oral HRT – with transdermal HRT the risk can be reduced [24, 25], even in patients with preexisting high risk like with factor V Leiden mutation [26], which also is the conclusion of a recent metaanalysis [27]. For venous thrombotic risk also the choice of the progestogen could be important [28]. The data suggest that progesterone and progestins from pregnane type may not enhance the thrombogenicity of oral administered estrogens (OR 0.7; 95 %-CI: 0.3–1.9) whereby pregnene derivatives may lead to a fourfold increased VTE risk (OR 3.9; 95 %-CI: 1.5–10.0). However, the important component seems to be the estrogen, and more data are needed to assess the risk attributed to the progestogen addition in HRT.

Risk of Breast Cancer – Main Mechanisms of Hormonal Effects

In contrast to cardiovascular risks it seems very clear that the main risk of breast cancer must be attributed to the progestogen component of HRT although at this time it is not possible to make conclusions on dependency of type, dosage and duration of the progestogen added to oral or transdermal estrogen therapy.

More than 60 studies on HRT and breast cancer have been performed [29], and there is no doubt that the risk can be increased with combined HRT, suggested in more than a dozen observational studies whereby mostly CEE combined with MPA or estradiol combined with norethisterone acetate in higher dosages have been used (reviewed [30]).

Until today the only placebo-controlled study, the WHI, demonstrated, that this risk is real if women are treated more than five years (HR 1.24; 95 %-CI: 1.01–1.54) [31]. But also with estrogen-only treatment an increased risk should not be excluded although this was not observed in the WHI (HR 0.77; 95 %-CI: 0.59–1.01) [4]. In compliant women there was even a 30 % significant reduction in risk of breast cancer (HR 0.67: 95 %-CI: 0.47–0.97), whereby the authors are discussing also mechanisms for this [32]. However, at least 20 observational studies with estrogen-only therapy or with not well-defined regular progestogen addition (as often usual in the earlier years) have demonstrated an increased risk [29], and mechanisms, as described as follows, seem to be plausible to explain this.

The main question, however, remains, if this increased risk, observed in clinical studies, depends on a causal relationship in so far, that estrogens, alone and/or in combination with progestogens, may lead to cancer cells and may lead to an increased incidence of breast cancer patients, independent of other factors.

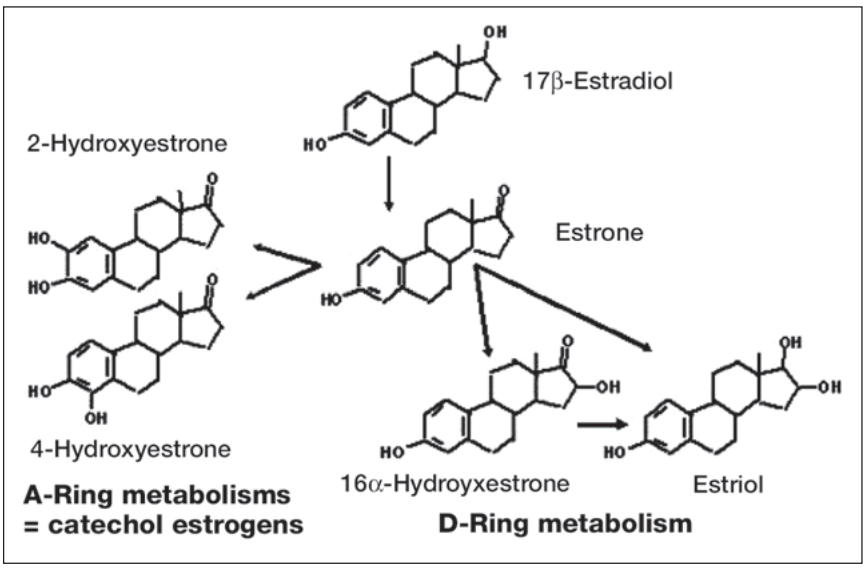

Figure 1: Estradiol metabolism

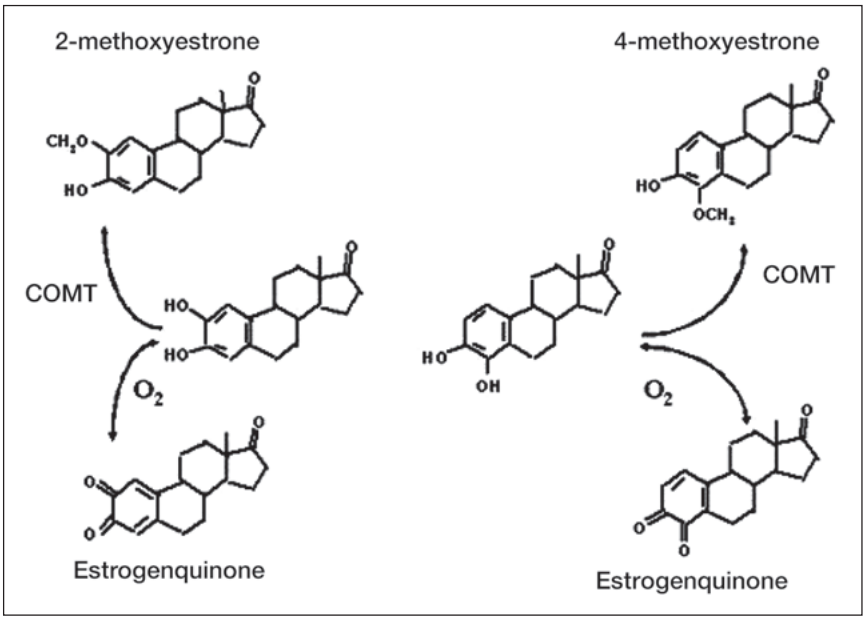

Figure 2: Subsequent metabolism of 2- and 4-hydroxyestrone, respectively. COMT: Catechol O-Methyl-Transferase

The World Health Organization (WHO), has defined estrogens and estrogen/progestogen combinations as "carcinogenic" [33]. With respect to the component of all HRT preparations, the estrogen component, two main mechanisms have to be considered for the discussion of a potential carcinogenicity in the breast. The first main mechanisms are proliferation/apoptosis effects on already pre-existing estrogen-sensitive cancer cells, which could end in a clone of malignant cells large enough to be detected as "breast cancer" in the clinical sense. This development needs at least 5–10 years according to the known doubling-times of most aggressive breast cancer cells. The second mechanism is derived from the fact, that estrogens can undergo excessive metabolism producing also biological very active substances, even in low concentrations, which may lead to genotoxic effects producing new cancer cells (Fig. 1, 2) (reviewed [34, 35]). Again, starting from those new cancer cells, to develop breast cancer clinically, the proliferation mechanisms would have to work for at least 5–10 years [36].

However, in special situations, also a decrease of breast cancer risk during hormones can be derived from those mechanisms, e.g. by antiproliferative or apoptotic effects or by producing carcinoprotective estrogen metabolites, which perhaps can explain the significant decrease of breast cancer evaluating women compliant to the estrogen only therapy in the WHI [32].

Both mechanisms involve that the risk can be increased by adding to estrogen certain progestogens. However, according to own experimental research [37–39], and likewise also in recent observational studies [40–43], there may be differences between the effects of progestogens in the breast with lesser risk using more natural progestogens like micronized progesterone or dydrogesterone, which is one of the most important topics of present research in the area of HRT.

And even if certain progestogens may increase the risk, it can be derived from experimental research, that this risk only would be true under very special, in general very rare conditions, correlating also with the low absolute excessive numbers of breast cancer in the range of 0.1–0.5 % assessed in clinical studies (like in WHI).

In general, progestogens down-regulate target tissue estrogen receptors which should lead to a down-regulation of proliferation mechanisms. However, certain progestogens have been shown to elicit strong effects on stroma-derived growth factors, which can have much stronger proliferating effects compared to estrogens, and there are differences in the actions in benign or malignant cells [37–39]. In addition certain progestogens may stimulate pathways of estrogen metabolism in the direction of potentially genotoxic metabolites [44].

The question for a causal relationship with breast cancer involves the production of new cancer cells followed by proliferation up to clinical detectable breast cancer. By proliferation mechanisms the production of a new cancer cell only seems to be possible in situations with disturbed reduplications of DNA leading to mutations, which indeed in in vitro experiments have been found in case of very rapid proliferation [45, 46]. However, a whole battery of mechanisms can work to protect from reduplication errors. Whether these proliferating effects on normal epithelial cells may cause malignant transformation has not as yet been proven, although DNA repair is hampered by activated proliferation [45].

Regarding the importance of the second mechanism, via potential genotoxic estrogen metabolites, currently research focuses on the possible carcinogenic properties of 4-hydroxyestrogens [47]. Animal experiments demonstrated a mutagenic effect of 4-hydroxyestrogen quinones [48]. Elevated 4-hydroxylase enzyme activity has been found in human breast cancer specimens, and 4-hydroxyestradiol as well as the quinones were found in high concentrations in human breast cancer tissue [34]. We were able to demonstrate that estradiol metabolism during HRT can be influenced by administration route and type of progestin, whereby transdermal application of hormones may avoid the development of potential genotoxic metabolites due to low dosing and avoiding of the first hepatic passage [44, 49].

The prerequisite for destruction and/or mutation of DNA by estrogenic "genotoxic" metabolites is that there has to be simultaneous cellular oxidative stress caused by additional factors like smoking or environmental factors, to produce radicals, which lead to adducts of DNA, and further via depurination to destruction of the DNA. However, biochemically the crucial reaction between semiquinones and quinones is a so called "one-electron-oxidation", and the cells are extremely well protected against this, because this may indeed lead to new cancer cells, demonstrated with well known carcinogens like benzene, hexestrol or polycyclic carbons [50–53].

The toxic effects of 4-hydroxyestrogens can probably be prevented under normal conditions by various cellular defence mechanisms. The quinones themselves can be inactivated by sulfocompounds, such as the ubiquitous glutathione. Intracellularly formed catechol estrogens are rapidly methylated by the enzyme Catechol O-Methyl-Transferase (COMT). However, for instance patients with a COMT defect due to genetic polymorphisms could be especially on risk of breast cancer during HRT, and similarly other polymorphisms of key enzymes in estrogen metabolites are discussed to increase the breast cancer risk, especially if there are cumulated defects. However, the clinical relevance still is under discussion, since those genetic changes are very rare [54, 55].

Conclusion

Hormonal therapy has been used for more than 40 years for treatment of climacteric and urogenital symptoms and/or prevention of osteoporosis. The only placebo-controlled study evaluating clinical endpoints in large patient samples has demonstrated an increased risk of venous thromboembolism, myocardial infarction, stroke and breast cancer, but cannot reflect practical conditions since patients on average have been too old for HRT, and about 50 % had the main risk factors like heavy obesity, hypertension and/or were smokers. Although in absolute numbers the risks are low (about 0.1 % per year), these risks may be important in women with additional risk factors or preexisting diseases.

There may be options to minimize those risks like use of transdermal HRT or individualized choice of the progestogen component, or use of estrogen-only therapy, possible in hysterectomized women or with endometrial protection by LNG-IUD. However, on the basis of biological plausibility regarding the underlying mechanisms perhaps no regimen can eliminate completely the risk of breast cancer during certain conditions like in women with already preexisting high-developed breast cancer clones and/or in women with defects in detoxification systems, e.g. due to genetic polymorphisms of key enzymes. Own and other new results of intensive research point out that additional factors are necessary to clinically develop breast cancer.

Thus there are important safety issues in hormonal therapy, but new options as well as new recent research suggest that on the basis of the WHI study the risks have been overestimated. Especially, if started early, in most patients the benefits should prevail, when indicated HRT is used properly.

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