Polymorphism diagnostics in HRT and HT-handling testosterone and estradiol RT risks

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The newest approach to Anti-Aging Diagnostics. Germany

Since the publishing of the WHI study and One Million study we are confronted with a totally new approach to the hormone replacement therapy or hormone therapy. Women and men ask more and more after a custom attracted and individualized HRT. We can observe a change of paradigm in nearly all medical subject areas. The standard of an individualized therapy for our patients requires more and more comprehensive epidemiological investigations, meta analyses and genetically analysis, which is especially supported by the detection of the human genome.

The aging process is characterised by a decline of most physiological functions. Among these the decline in endocrine functions plays an important role in the symptomatology of the aging process. Clinical and epidemiological studies, along with basic scientific research, have shown a trend toward androgen deficiency in aging males.

In contrast to women with the rather abrupt termination of the ovarian cyclic hormonal activity, in men both endocrine (testosterone) and exocrine (spermatogenesis) testicular functions are preserved until very old age. Hence, the male equivalent of the menopause, the andropause does not really exist. Nevertheless, both endocrine and exocrine function decline with age.

Testosterone

A couple of complaints are found during the age related declining testosterone production. They include age-related disturbances in memory, muscle mass, and strength. Clearly, loss of libido and impotence may be testosterone effects, and osteopenia may be another. There is evidence to suggest that disturbances in balance and declines in maximal oxygen uptake capacity (VO_{2max}) are also related to declines in testosterone levels, although these effects have been understudied. Changes in food intake may also be effects of testosterone loss. Male sexual function declines with age. It is now clear that the decrease in T levels as a function of age has both a testicular and hypothalamo-pituitary origin, but Leydig cell function decreases not always together with increase of pituitary hormone LH. However, in elderly men, the LH levels are frequently not increased or only modestly increased, a consequence of the alteration of neuroendocrine control of gonadal function. Moreover the circadian rhythmicity of LH and T secretion is blunted in elderly men and the amplitude of LH pulses decrease. The effects of androgens in men and women are very similar and different. (interest in sexuality, sebum production, hair growth and loss, Epo- production, improvement of lipid profile in men, but not in women. Being a source for estradiol stimulating bone cells, effecting muscle and fat mass. Controlling CYP 19 P450 gene polymorphism (Aromatase) has a great impact of the prevention of supraphysiological estradiol levels and the bone density.

Whereas it has long been debated whether plasma testosterone (T) concentration decreases with age in healthy men, the occurrence of an age- associated decrease in bioactive testosterone concentration is no longer disputed. Normal plasma T levels range vary between 11 and 40 nMol/L and reach their maximum at 25 to 30 years. Testosterone circulates in plasma bound for about 50% to Sex Hormone Binding Globulin (SHBG), a β-globulin with high affinity but limited binding capacity for T and is bound for about 50% to albumin (low affinity, high binding capacity). In young healthy males, the plasma FT

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concentration varies between 0.2 and 0.7 nMol/L. Due to the high binding affinity of SHBG, only the free and part of the albumin bound T is bio available. The significance of SHBG bound testosterone is poorly understood. It has been shown, that some tissues (prostatic cells) carry SHBG receptors, the activation which leads to stimulation of cyclic AMP.

Today scientists are looking for hormonal substances that will rejuvenate human beings and allow them to live longer. Can this be done with testosterone? Probably not, but the full range of its potential may be under appreciated. Twenty years of clinical experience and current research findings provide a convincing argument that testosterone replacement has a role to play in improving the quality of life in older men.

Testosterone deficiency in men is manifested typically by symptoms of hypogonadism, including decreases in erectile function and libido. 25 % of men over 65 have subnormal T levels. Testosterone also has an important role in the regulation of normal growth, bone metabolism and body composition. Specifically, testosterone deficiency is an important risk factor for osteoporosis and fractures in men. In men older than 65 years of age, the incidence of hip fracture is 4-5/1000 and approximately 30% of all hip fractures occur in men. Men with testosterone deficiency have significant decreases in bone density, particularly in the trabecular bone compartment. Testosterone deficiency has been reported in over half of elderly men with a history of hip fracture. Men with testosterone deficiency also have alterations in body composition that includes an increase in body fat. Using quantitative CT scans to assess fat distribution, we have shown that testosterone deficiency is associated with an alteration in site-specific adipose deposition with increased deposits in all areas particularly in the subcutaneous and muscle areas. Because truncal fat correlates with glucose intolerance and cardiovascular risk, hypogonadism may have important implications with regard to overall health and mortality. In one study, the alteration in skeletal muscle composition was associated with a decrease in muscle strength. Therefore, testosterone deficiency is associated with an enhanced risk for osteoporosis, altered body composition including increases in truncal fat, and possibly, decreases in muscle performance.

Administration of adequate testosterone replacement therapy leads to improvements in libido and erectile function. Following testosterone replacement, men note an increase in energy and mood, which may reflect either direct behavioral effects of androgens, and/or, an elevation of hematocrit due to rising testosterone levels. Testosterone therapy also leads to important beneficial effects on the skeleton and lean tissue mass. Testosterone replacement increases bone density in hypogonadal men with the most dramatic effects seen in the trabecular bone compartment. These effects may be seen as early as 6 months following initiation of testosterone therapy. In one recent study of the long term benefits of testosterone therapy, the greatest benefits in trabecular bone were seen in the first several years of therapy. With regard to body composition, testosterone replacement therapy results in a dramatic reduction in adipose content, with the greatest effects seen in the subcutaneous and skeletal muscle areas. Androgen therapy leads to a significant increase in lean skeletal muscle mass and strength. Therefore, there are beneficial effects of testosterone replacement on body composition and bone mineral density in adult hypogonadal men that may serve as indications for therapy in addition to libido and sexual function.

Estrogens

With a life expectancy of 81.2 years, many women may live up to 30% of their lives after menopause.[1] Presently, 12.6% of Canadians are over the age of 65, and of those, 58% are women. By 2051, 25% of Canadians are expected to be over age 65.

Sexual hormones display an essential importance for reproduction and later in life for the metabolism, the cardio-vascular system, and the well being of the postmenopausal women. After menopause, which means an dramatic decrease of estrogenic secretion, accompanied by the lack of progesterone and androgens starts a multiple lost of functions, especially in the brain area(central vegetative neuronal system, psyche, libido, cognition, memory), bone, skin, connective tissue, peripheral vessels and cardio-vascular system. Health concerns of the postmenopausal patient include cardiovascular disease, osteoporosis, breast cancer, genitourinary concerns and menopausal symptoms.[2] It has long been thought that estrogen impacts the brain and central nervous system, vasomotor stability, breasts, mood changes and cognitive function, and its loss contributes to urogenital atrophy, bone loss and cardiovascular effects.

At the end this changes of ovary secretion weaken those systems with the endpoint of MI, apoplexy, increased

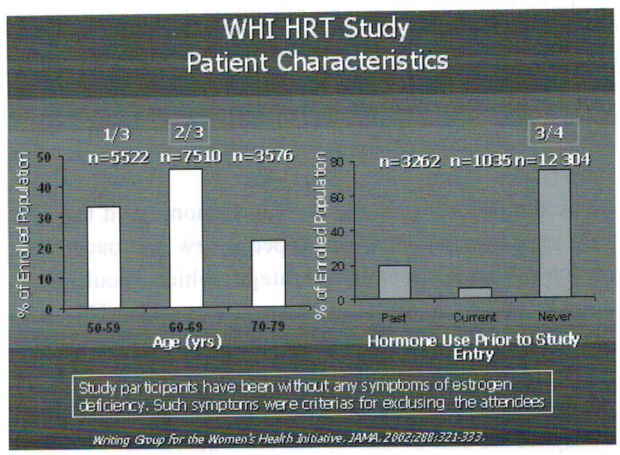
oxidation and weakened lipid metabolism with high cholesterol levels and increased Alzheimer disease. More than 100 years ago Osler noted that heart disease was entirely a disease of men. Fifty years ago, the most popular explanations of sexual difference in heart disease were particularly cigarette smoking, or differences in stress. The results between and within populations and consistent across risk factors support the hypothesis that women are protected by an intrinsic factor, presumably female sex hormones (Barret- Connor, E) Several types of epidemiological evidence suggests that women's universal protection against CHD is explained by estrogen.
The main observations are that CHD is

- uncommon in women before the age of menopause
- more women in women who have a prematurely menopause
- more common in young women who have both ovaries removed
- less common in women who receive HRT after menopause

From that point of view it seems to be consequent to consider a long term HRT with progestins and estrogens The last years we had been opposed to a lot of data, resulting from studies which at least came to the conclusion that the risk of a ERT, composed with progestins displays a higher risk than benefit for the HRT using women. (HERS,HOPE, WHI, One Million Study). This was in contrast to the findings of other studies, which praised the benefit of HRT.

Whether women are taking hormone replacement therapy for the prevention of heart disease, osteoporosis or the symptoms of menopause, results from the Women's Health Initiative (WHI) study have brought to the forefront many concerns. Results from this as well as the HOPE study are reviewed, followed by the ensuing responses and recommendations from medical societies. Assessing and tailoring hormone replacement therapy for every woman individually is what can be recommended clearly until further studies are published. In 1998, the Heart and Estrogen -Progestin Replacement Study (HERS) highlighted the impact of HRT in postmenopausal women with documented coronary heart disease (CHD).This blinded, placebo-controlled study included 2,763 postmenopausal women with coronary disease and an intact uterus, younger than 80 years and with an average age of 67 years. Women were randomized to either 0.625mg of CEE plus 2.5mg MPA in one tablet daily (n=1,380), or a placebo of identical appearance (n=1,383). After an average follow-up time of 4.1 years, analysis of data showed a higher risk of coronary events in the hormone group during the first year. This risk was reduced after years three to five. At the end of year one, the rate of CHD events in the HRT arm was 42.5 compared to a rate of 28.0 in the placebo group, giving a relative risk (RR) of 1.52. After years four and five, the numbers were 23.0 and 34.4, respectively, with a RR of 0.67. The major outcomes of the WHI study were higher rates of stroke (41%), invasive breast cancer (26%) and cardiovascular disease (29%) among the women taking HRT, and a twofold increase in venous thromboembolic events in the treatment arm. There was a 37% decrease in risk of colorectal cancer and a 33% reduced risk of vertebral and other osteoporotic fractures with HRT usage.

It seems to be, that the results of WHI and HERS showed the typical problems of a not individual, custom-tailored HRT, which leads to problems in a definite percentage of the female population, who have shown mostly because of genetically reasons, or lifestyle reasons alterations in their steroid-hormone metabolism, which leads to higher risks of CVD and cancer, especially of the breast and endometrial mucous membranes.



The very interesting overview by M. Clemons and P. Goss published in 2001 in the New England Journal of Medicine [1] and their presented studies substantiate the assumption that the continued increased burdening of the organism by supraphysiological doses of 17-β Estradiol increases the proliferation pressure of the mammary glands, increases the radiological density of the mammogram and at least increases the lifetime risk of breast cancer.
Therefore it seems necessary to maintain low estrogen levels at the systemic level or by the paracrine way. This

efforts to maintain the estrogen concentrations in the sex-steroid dependent tissues as low as possible is a demand on the evidence based medicine. The breast cancer risk depends on the cumulative risk of lifetime estrogen exposition[2,3,4]. The demand after estrogen replacement bases on the experience, that estrogens have a positive influence on a lot of age-related health-risk developments, especially on the support of bone metabolism, and the improvement of the lipid profile, which can affect the CV risk.

17-β Estradiol effects directly on the genome, bound by estrogen receptor complex. This has impact on the effects of supraphysiological increased Estradiol levels and the cell metabolism, cell division and transcription of the DNA. Therefore should the practised HRT of administering female sex steroids without knowledge of the production and breakdown of Estrogens and other sex steroids hormones, especially the genetically dependent influence of the steroid metabolism belong to the past.
Since we know that the difference between individuals is based on genetic mutations and polymorphism, the HRT managing physician should use

1. personal history dates (weight gain in pregnancy, endometriosis, breast cysts, ovarian cysts, prostate risks, BPH)
2. clinical profile, hormone plasma tests (high Estrone, Estradiol levels, high DHT and testosterone levels)
3. images producing methods like bone density scan (high bone density), mammogram (high tissue density) and ultrasound (cysts, high endometrium)

Since the decoding of the Human Genome and the new chip technique we have developed a new approach to an endocrinological treatment strategy, which should be 1. individual, 2. custom attracted and 3. secure. The great advances in medicine in the last years can realize this idea for the near future.

Today we are able to answer this main questions:

- **Cardiovascular diseases:** Who will get the most profit by using hormone replacement therapy?
- **Thrombosis :** Which patient will be reckoned to the risk of clotting and CV- complications .
- **High tissue and blood - levels of Estradiol, Testosterone and Dihydrotestosterone:** How can we avoid supraphysiological hormone plasma levels, which have been recognized to a high risk for breast cancer and prostate cancer?
- **Neurological age related diseases as Alzheimer, Parkinson**
- **Oral versus transdermal therapy- Custom tailored Hormone Therapy**

4. polymorphism diagnostics : SNPs determine the phenotype
5. Epigenetics

to estimate and calculate HRT doses in an individual manner and to avoid possible risks by designing a custom tailored therapy.

To estimate the Benefit of HRT in men and women the following polymorphisms give us a possibility:

Cardiovascular risk

While environmental factors such as diet, physical activity, and alcohol intake play an important role in determining triglyceride levels, results from family studies have all suggested a strong genetic component to triglyceride levels. Although family members tend to share a similar environment, studies on twins reared together have shown that triglyceride levels are highly influenced by genetic variability. However, considerable inter-individual variation is observed in the response of LDL and other lipoproteins to dietary change. The hypothesis that genetic differences contribute to this variability has led to several studies in which associations of dietary lipoprotein responses have been sought with polymorphisms in genes affecting lipoprotein metabolism[17] .
There is increasing awareness of the potential for genetic variation among individuals to influence nutrient requirements and biological responses to nutrient intake. In the case of genes influencing LDL subclass patterns, gene-diet interactions contribute to wide inter-individual differences in the effects of low fat, high carbohydrate diets on risk for coronary heart disease. The degree of the inter-individual differences may be magnified in certain genetic sub-populations. Some of these sub-populations will likely be ethnic minorities. The recognition of such differences in metabolic response is prompting greater appreciation of the concept of intelligent nutrition based upon knowledge of nutritional status, nutritional requirements, and genotype.

Inflammation

Aging is a chronic inflammatory disease leading to the

cardiovascular diseases, Alzheimer D. and Cancer, as well as Parkinson Disease (IPS).The(Interleukin) IL 10 CC 1082 is associated with increased production of IL 16 and highly represented among centenarians. The IL G>A 1082 genotype is correlated to a higher pro inflammatory state.

Plasminogen Activator Inhibitor-1 (PAI-1) Polymorphism

In contrast to the 5G allele the 4G Allele of this gene is associated with reduced fibrinolytic activity. In thess cases the PAI-1 level in blood samples is increased. This displays an increased risk for thrombosis and CHD. In combination with other clotting factor risks (MTHFR, Prothrombin Factor II, Factor V Leiden) we find a multiplicated risk. Estrogens can decrease PAI-1 in women.

The physiological role of PAI consists of the inhibition of the plasminogen activator. The plasminogen activator stimulates the conversion from plasminogen to plasmin an antagonist to thrombin in the blood coagulation cascade. A polymorphism in the promoter region of the PAI-1 gene causes increased PAI-1 levels. This causes a reduced thrombolysis and fibrinolysis. Estrogens decrease the PAI-1 levels in women. Obesity and homozygous carrier ship increases the disposition of CV diseases and insulin resistance. The 5G/5G genotype has been found primarily in slender persons in contrast to the 4G/4G genotype. Patients with 4G14G genotype have been found to display a 3-5 fold increased risk for obesity, heterozygous ones have a doubled risk. On the other hand there is a decreased tumor risk, because plasminogen has been found to be converted to Angiostatin, one of the most powerful angio - neogenese factors in tumours. The correlation of PAI-1 mutation and MTHFR or factor V, glycoprotein IIIa or Prothrombin factor II is evident and has an additive, if not cumulative affect. Oral Estrogens decrease the PAI ?1 levels.

Prothrombin Factor II F2

A vitamin K dependent blood clotting factor, which leads to increased risks of blood clotting, if there is an increased expression of factor II F2 by mutation of the F2 gen (G20210 aA). (Psaty et al. JAMA 285(7):906-13,2001). The conversion of prothrombin (also called factor II) to thrombin is a key event in blood coagulation. The human gene encoding prothrombin, F2, contains a rare polymorphism within the 3'-untranslated region, which is known to cause elevated serum prothrombin levels, leading to a "hypercoagulable" state, that is reflected in a ~2-5 fold increased risk of venous thrombosis. Beside its role as accepted risk marker for venous thrombosis, the F2 variant is a weak genetic risk marker of arterial ischeamic events. The polymorphism is a contraindication for estrogen or testosterone replacement.

MTHFR-Polymorphism

A very frequent polymorphism in the Methylentetrahydrofolate gene causes a thermo labile enzyme variation. This causes a diminished capacity for the break down of the amino acid methionine. Carrier with homocygoty of the mutant V/V gene- type display increased homocysteine concentrations. This genotype is found in populations with CHD twice fold frequent than in healthy controls. Due to thrombosis risk there is an additive effect of Factor V Leiden. As one displays a homocygoty of this gene mutation, he has an increased risk for Stroke, myocardial infarction, breast cancer and aneurysm: The solution of prevention is: a daily intake of Vitamins B12, B6, folic acid and trimethyl glycine. The methylation process is an enormously important part of gene regulation, break down and elimination of hormones and their metabolites (COMT: below), as well as neurotransmitter elimination. In so far it seems to be of very important need to watch demethylation during the aging process. Further methylated amino acids can help to improve methylation: S-Adenyl-methionine, Cysteine, N-.Acetyl-Cysteine. They all are sulphur carrying amino acids, participating very much in the Glutathione supported antioxidative and detoxification systems.

This mutations in homozygous variant has been found to increase the risk for prostate and breast cancer as well, probably due to the impaired methylation activity of the Androgen receptor gene.

Factor V (Leiden)

The G 1691A-mutation of the F5 Gen is known to cause the activated protein C resistance. (APC resistance)

The carrier of this mutation has a high risk for thrombosis.

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The average incidence of venous thromboses is about 1:1000. Reason for that is the resistance of factor V against APC and increased Prothrombin levels. 50% of all patients with thrombosis have this factor V Leiden polymorphism. You display a lifelong increased risk for thrombosis. About 4-6% of the population are carriers of your polymorphism factor V. High risk factors are : smoking, alcohol, contraceptive pills and HRT.

Glycoprotein IIIA Polymorphism

This Protein belongs to Fibrinogen-and Vbitronectin receptor and disoplays a pre- coagulation effect. A variant of the GPIII"a" gene (PIA1/PIA2-Polymorphism) has impact on the basic risk of coronary heart disease and influences the developing disease. Glycoprotein IIIa, a subunit of the platelet membrane receptor (GPIIb-IIIa) for fibrinogen and von Willebrand factor, has an important role in platelet aggregation. Molecular studies have consistently shown that a particular polymorphism, PlA2, increases platelet responsiveness, suggesting that this variant might be involved in the pathogenesis of acute coronary syndromes. In a meta-analysis from 12 epidemiological studies, this polymorphism was associated with an increased risk of coronary artery disease. High Risk: HRT, Contraceptive Pill, Testosterone replacement.

Endothelial NO- Synthetase

NOS3 has its effect on Vasorelaxation. A mutation of the promotor region of the NOS3 gene reduces NO and is related to coronary spasms and hypertension. It displays a higher risk for myocardial infaction and hypertension. In the vascular system, nitric oxide (NO) plays important roles by exerting vasodilatation, regulating blood flow and systemic blood pressure, and by conferring thromboresistant and artery-protective properties to the endothelium. Endothelium-dependent vasodilatation is mediated by release of NO formed by endothelial nitric oxide synthase (eNOS). A reduction in NO synthesis or availability might underlie impaired endothelium-dependent vasodilatation observed in blood vessels of individuals with cardiovascular risk factors, such as active and passive smokers and patients with hypertension or hypercholesterolemia. Loss of NO-mediated effects may further predispose to the development of arteriosclerosis.

Estrogens and Testosterone can increase NOS3 activity.

Apo E2/3/4 polymorphism

Apo E4 (Frequency 17%) is correlated with high LDL and low HDL-cholesterol levels (type V) Carrier of this mutation display a pre- dsiposition fpr Alzheimer disease (late onset) .Apolipoprotein E (ApoE) is a protein component of several plasma lipoproteins, including triglyceride-rich chylomicrons and very-low-density lipoprotein (VLDL) particles. As a ligand for the low-density lipoprotein (LDL) receptor, ApoE plays a major role in plasma lipoprotein metabolism. Two SNPs within the human APOE gene form 6 common genotypes, leading to 3 major isoforms of ApoE, ApoE2, -E3, and -E4. The genotypes are as follows (according to their frequency): E3/E3, E3/E4, E3/2, E4/E4, or the very rare E2/E4, and E2/E2 genotypes. Carriers of the ApoE4 allele have higher levels of total and LDL cholesterol and therefore have a higher risk of cardiovascular disease. Further, the ApoE4 allele has been related to dementias, most commonly Alzheimer's disease. Estrogens and Testosterone have an positive effect on slowing down the Alzheimer risk.

G Protein Beta 3 subunit

This common polymorphism is associated with enhanced activity of signaling pathways of a multitude of hormones (like insulin and neurotransmitters). In the cardiovascular system, this polymorphism primarily affects vascular reactivity and cell growth of cardiomyocytes. The variant allele has been associated with obesity and hypertension.A homozygous genotype for the variant allele (T/T) has been detected. In hypertension, the 825T variant allele is associated with low renin activity and appears to strongly predict the development of left ventricular hypertrophy. This variant allele is further associated with the development of obesity, in particular in young people (age 18-30 years). This effect is most pronounced in combination with an unfavorable lifestyle, characterized by high-caloric fat-enriched nutrition and low physical activity. In general, the odds ratio (T/T genotype versus C/C genotype) for overweight is estimated ~2- to 3-fold. Carriers of the 825T variant are at higher risk of **obesity** and **hypertension** and are, if applicable, candidates for favorable life-style. Estrogen therapy can support the worse effects of this polymorphism. Testosterone has beneficial effects on lipolysis.

Bone Density: Testosterone for men, Estrogens for Women? Vitamin D beyond the bone protection: protecting breast and prostate

Vitamin D3.Receptor Mutation (VDR)

The VDR has directly influence on the Calcium absorption in the intestinal tract and on the Calcium input into the bone-tissue.

A polymorphism of the VDR gene (Bsml-RFLP) correlates with an increased bone density and a diminished fracture risk in spine, hip and legs. In that case a HRT in order to protect the bones from loosing its density is not necessary.

The homozygous variant is close correlated to an increased

prostate or breast cancer risk due to the Vitamin D protecting effect directly at the DNA replication cycle.

Breast and Prostatic Cancer-Risk

Hormones as all medicaments and environmental toxins are converted and eliminated by enzymes. The genetically code of them can give us an information about the enzymatic activity, which can cause accumulation or fast elimination. To understand your results you should know, that each gene consists of two alleles, one from mother, one from father. Depending if the mutation is found in both alleles (homozygoty) or only in one of them (heterozygoty) is important for the phenotypically expression and at least for your personal risk.

Knowing polymorphisms of the genes of steroid metabolising enzymes gives us possibilities to estimate the risk of not familiar-dependent breast cancer.

The combination of personal history, Mammogram (high density), ultrasound (ovarian cysts, high build up Endometrium) and bone density (increased bone density leads to the suspicion of elevated lifelong estradiol levels.

The breast cancer risk depends on the cumulative risk of lifetime estrogen exposition.[2,3,4]

The Progesterone receptor

HPR + 331A : increased transcriptional activity and increases the hPR-B encoding transcript. Contribution to breast and endometrial cancer not by loss of progesterone antiproliferative activity, but by increased transcription. This finding poses a paradox as high activity progesterone receptors should work antiproliferative, but it explains the result of the WHI study, with higher risk in the Estrogen ?Progestins group (MPA). Highly malignant forms of endometrial, cervical and ovarian cancer have been found with overexpression of PR-B. Its likely to be working in a concert with estrogens, xenobiotics, and extra ovarian estrogens, converted by aromatase.

Cytochrome P450 17 alpha Hydroxylase (CYP17)

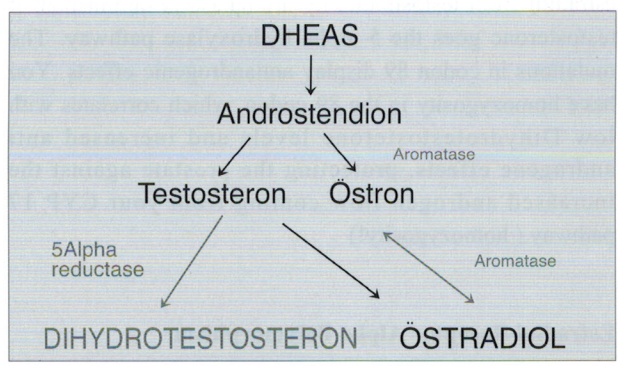
CYP 17 decodes a key enzyme of the steroid metabolism, the 17 alpha Hydroxylase. This enzymes act converting Pregnenolon and DHEA to Androstenedione. Polymorphism in this gene causes increased androgen levels in the tissue and in so far an increased risk for prostate and breast cancer. The CYP 17 T-34-C mutation in the promoter region of this gene, correlates with increased Testosterone levels, and diminished need for Testosterone in men's HRT. Men with this mutation are urgently recommended not to take DHEA, and to keep their TRT dose very low, perhaps on alternating days. They should undergo urological exam, PSA and sonogram on a regularly base.

Men with this mutation display higher risk of prostate cancer and should keep their testosterone dose in HRT low. They should undergo regularly urological exam of the prostate and measure their PSA.

For men we recommend :

Vitamin E 400 IU
Selen 100 mcg
Lycopen 30 mg
Vitamin D3 800 IU
Indol 3 carbinol
Soja

Women display higher androgen levels, if they don't have an aromatase polymorphisms. In the case of combined CYP 17 and aromatase snp (CYP 19) DHEA will be converted very fast to androstenedione and to estrone. This decreases the need for estrogens in postmenopausal women, but increases the breast cancer risk. A protection of breast cancer is high androgen levels. Women with a CYP 17 mutation and a joint SRD 5 Alpha mutation convert androstenedione very fast to Dihydrotestosterone (DHT). This would be a protection, especially if the Androgen receptor has a high androgen sensitivity, following the CAG AR-polymorphism (loss of CAG repeats).



P450 Cytochrome 19 Gene, Aromatase

Of great importance is the knowledge of the activity of the aromatase, which is coded by the CYP 19 gene. High

activity of this enzyme leads to a faster conversion rate from testosterone to estradiol and from androstenedione to estrone, which at least increase the estrogen tissue- and plasma levels. We know several polymorphisms of this gene, which all are of great practical importance. The C 1558 T Mutation doubles the risk of breast cancer (OR 2.0 , 95% KI 1,3 -3,1), another CYP 19 Mutation decreases significantly the risk to get breast cancer over lifetime.(OR o, 39, 95% KI- 0,17- 0,89) Your homozygoty is correlated to benign prostate hyperplasia and obesity, breast growth, fluid retention. Positive effects are observed on the intra endothelial aromatase activity, increasing estrogens in the endothelium and by this causing a stimulation of the Nitric Oxide Synthase (NOS 3) to relax the coronary vessels and decrease the vessel tonus. It is recommended to ingest aromatase inhibitors like Genistein, isoflavones from red clover, hops, soy, zinc, selenium and Arimidex.

SRD 5A2 Gene Polymorphism of the 5 Alpha Steroid Reductase

The Enzyme 5 Alpha Reductase type II catalyses the formation of Dihydrotestosteron from Testosterone. This enzyme consists of variants (Arg49Thr and Val89Leu), of which the Codon 89 Polymorphism reduce the androgen levels by decreasing the 5 Alpha Reductase activity and has anti-androgenic effects. In contrast the wild type (WT) Val/Val or Arg/Arg decoded enzymes cause for increased activity. Especially the codon 49 polymorphism increases in homozygosity the DHT levels and is responsible for a proliferation pressure together with the growth factors TGF-1, EGF, SMGF. In this special case men display a higher risk for prostatic cancer, women decrease their risk for breast cancer because the amount of newly formatted estradiol from testosterone by aromatase is diminished, if testosterone goes the 5 alpha hydroxylase pathway. The mutations in codon 89 display antiandrogenic effects .You have homozygosity in the 89 codon, which correlates with low Dihydrotestosterone levels and increased anti androgene effects, protecting the prostate against the increased androgen flow coming from your CYP 17 pathway.(homozygosity!)

Estradiol Receptor Alpha Polymorphism:

Postmenopausal women with coronary disease who have ER-alpha IVS1-401 C/C genotype, or several other closely related genotypes, have an augmented response of HDL cholesterol to hormone-replacement therapy (34)

The break down and eliminating of estrogens:
Phase I
CYP 1A1 and 1B1 gene Polymorphism:

This type of genes codes for the 2 major enzymes controlling the break down of estrogens and xenobiotics from toxic environment. Mutations in those genes lead to higher levels of Estradiol and increased pressure on the proliferation of female hormone dependent tissues. Further moire it cuts the estrogens to form 2 OH-Estrogens and 16 OH estrogens. Estrogens are converted, before being eliminated to C16 and C2, C4 intermediary products. They can be diagnosed in the 24 hr urine. In this case, if you having been examined these C2/C16 products, the ratio between them is very important, because 2 OH-Estrogens are associated with higher risk for osteoporosis and cardiovascular disease and 16-OH estrogens with higher risk of breast cancer.

Break down products of estrogens play a major role in the formation of carcinogenic cells. This correlates to the female reproductive organs and their breast glands as well to the benign prostatic enlargement.

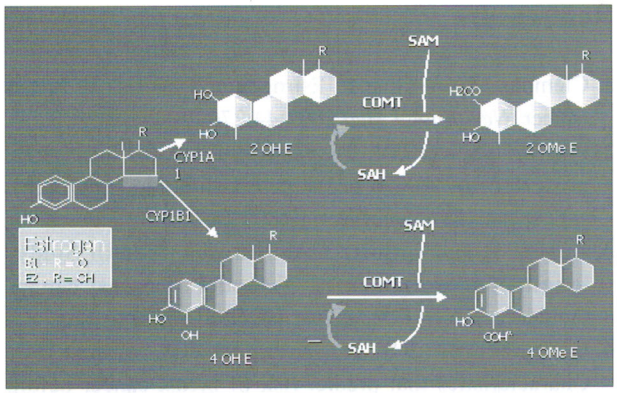
Especially the C16 OH- intermediary products from phase I of the break down process display a high carcinogenic potential, if their concentration is high in the cell and the time the cell is under the growth pressure of this hormones is long enough. C16 products of estrogens cause stimulation of cell division.

The genes CYP 1A1 and 1B1 are responsible for the elimination of all estrogens, some toxic substances coming from the inner body or from outside. CYP 1A1 also acts in eliminating some contents of tobacco smoke like benzopyren and other polycyclic hydrocarbons, who have carcinogenic effects on the DNA.

To eliminate C4, C16 and C2 fast, they have to be linked to other enzymes, as COMT and Sulfotransferase (phase II) which convert them to water-soluble products, which can be eliminated by the kidneys.

The main breakdown products of the estrogen metabolism are 2OH estrogen and 16 OH estrogen. 16 OH estrogen displays very strong estrogenic effects and is evidenced by a lot of studies done, with breast cancer risk. In contrast to 16 OH E, 2 OHE displays rarely estrogenic effects. The ratio 2/16 gives us an overview over the estrogen metabolism.

A ratio from 1.5-3.0 is said to be fine for you. The higher the ratio, the higher the risk for osteoporosis, cardiovascular disease, depressive and menopausal syndromes.



Removing Estrogens and Xenoestrogens by CYP 1A1 and CYP 1B1 (step I) and COMT (step II) Stimulation of COMT with folic acid and S-Adenyl-Methionin (methyl donator)

The lower or inversed this ratio is, the higher the risk for breast cancer, uterus cancer, Lupus Erythematodes and chronic polyarthritis.

PHASE I

CYP 1A1 :

Cytochrome 1A1 mediates the elimination of Estrogens by C2 hydroxylation and metabolises environmental toxins (pollution) as well as polycyclic hydrocarbons. Polymorphisms in this gene can affect the breast tissue by increased C2- OH products. Two mutations in codon T6235C and 462 are associated with an increased breast cancer risk. Smokers have a 5 fold risk because of the parallel effects on this enzyme, which eliminates carbon products by hydroxylation as well.

Populations in western countries, who smoke have a 9 fold risk! (OR 9.7; 95%-CI 2.0-47.9)

An increased break down of estrogens by CYP 1A1 leads to a high CYP 2OH/CYP 16 OH ratio, a slowed break down to an increase of C16 OH products, which have a high proliferate and carcinogenic effect on the tissue. You have 2 mutations: stop smoking, no estrogens and inhibit the activity by :increased alimentation of cabbage like broccoli, cauliflower, brussel sprouts, red and yellow garden vegetables, Inbdol-3 Carbinol capsules, flax seed, . In case of a CYP 1B1 mutation it is worth, to measure the NAT2 and GST activities (2. step)+COMT and Sulfotransferase. No smoking, avoiding smoked nutrients, paintings, chemical pollution and petrol gases is very important, because they are in competition with estrogens and by themselves producing high reactive intermediary products they are carcinogenic.

CYP 1B1

An accelerated hydroxylation of estrogens by a CYP 1B1 polymorphism causes a high 2/ 16 ratio, as CYP 1B1 hydroxylates estrogens in C 16, which leads to osteoporosis and estrogen deficiency over the sexual life span. Increased CYP 16 activity increases the 16 OH estrogens which are high proliferate and cancerogenous. CYP 1B1 eliminates all cyclic hydrocarbons, , Benzopyren, aflatoxins, dioxins, from paintings, gas, petrol, smoking, BBQ products. Avoid the exposition to these toxins. Inhibit the activity by increased alimentation of cabbage like broccoli, cauliflower, Brussels sprouts, red and yellow garden vegetables, Inbdol-3 Carbinol capsules, flax seed, . It is workfolk, in case of a CYP 1B1 mutation, to measure the NAT2 and GST activities (2. step)+COMT and Sulfotransferase. A ratio from 1.5 + 3.0 is said to be fine for you. The higher the ratio, the higher the risk for osteoporosis, cardiovascular disease, depressive and menopausal syndromes.

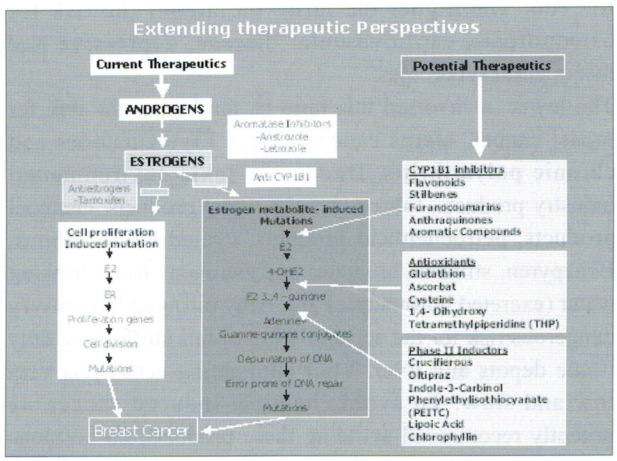
The lower or inversed this ratio is, the higher the risk for breast cancer, uterus cancer, Lupus Erythematodes and chronic polyarthritis. Due to the toxic environmental industry products, tobacco smoke, BBQ products, charcoal products, petrochemical products, cycled hydrocarbons, Benzpyren, stilbene, aromates and estrogens from drinking water (excreted hormones of anti-baby pill) you have a very dangerous risk for the accumulation of this stuff in the fatty tissue depots and liver. Your eliminating activity is very low and slow. To avoid chemical induced cancer we urgently recommend avoiding these products, no hormone replacement therapy, stimulating the enzyme activity by nutrition: add to your normal diet cabbage as broccoli, cauliflower, green and yellow vegetables. Capsules with Indol-3-Carbinol, flaxseed, Omega 3 fatty acids.

Catechol-ortho-Methyl-Transferase (COMT) and CYP 1A1, CYP 1B1

The COMT is responsible for the breakdown of catechol-estrogens by methylation (see above MTHFR), which are the intermediary products of estrogen break down, converted from Estrogens by P450 oxidases (Cytochrom P450 1A1 (CYP 1A1) and (P450 CYP 1B1). This intermediary produced catechol -estrogens display high cancerogenous potency.

Polymorphisms of CYP 1A1-gene leads to increased levels of estrogens and catechol ? estrogens, which are themselves

a great risk for the development of breast cancer.
Mutation of the COMT gene leads to a slower breakdown rate of catechol-estrogen so that this increased amount of cancer stimulating intermediary estrogen products is available in the breast cells. Folic Acid is urgently needed ! Avoid alcohol due its additive effect on the enzyme deficiency, eventually switch to phytoestrogens or Tibolone.
Men have a higher prostate cancer risk, because the loss of methyl groups of the epigenetic sequence of the androgen receptor.
Folic acid, exercise, weight loss, low carb diet, low fat diet, plenty of vegetables (green-yellow ones), Vitamin E, Vitamin D3 800 IU, and selenium 100 mcg should be added to diet!.
Evista and other SERMs (Isoflavones) can be a better choice than estrogens in case of a homozygous mutation in this gene.



In a 2001 publishes study by Ritchie et al. the risks for breast cancer in a multifactor dimensionality was calculated. This is a very good model for the estimation of the patients' risk. This MDR is a powerful alternative to traditional parametric statistics such as logistic regression.

TGFBR1 6A and cancer

This polymorphism shows the following:
Overall cancer risk is increased for heterocygoty (19%) and for homozygoty (70%).
TGFBR 6A carriers have an increased risk for cancer of 24% (Odds ratio 1.24, CI 95%, 1.10 - 1.40)
The risk of breast cancer is increased by 38%, ovarian cancer 41%, Colorectal cancer 20%.(31, 32)

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