



EstroGenomic[™] Profile

Understanding Health Risks in the Post-Menopausal Woman

- The EstroGenomic[™] Profile is targeted to peri- and postmenopausal women, as well as premenopausal women considering oral contraceptives
- The profile includes single nucleotide polymorphisms (SNPs) which relate to menopause-associated health risks and the varying effects (both good and bad) of hormone therapy (HT). All selected SNPs have been researched in terms of their interactions with HT; commentary helps the practitioner weigh the risk/benefit ratio in a particular area.
- Subsections of the profile include risk markers for estrogen metabolism (relates to sporadic breast cancer), hypercoagulation, cardiovascular disease, and osteoporosis
 - Estrogen metabolism SNPs focus on the Phase 1 enzymes involved in the formation of anti- or procarcinogenic metabolites such as 2-OHE1 and 4-OHE1, respectively, as well as the Phase 2 enzymes responsible for the subsequent metabolism of these compounds.
 - Hypercoagulation markers relate to estrogen's interaction with some of the key constituents of the coagulation process, including clot formation and clot degradation (fibrinolysis).
 - Cardiovascular markers touch on areas such as HDL- and LDL-cholesterol, inflammation, and homocysteine
 - Osteoporosis SNPs relate to estrogen's influence on inflammation, bone resorption, vitamin D, and collagen formation

Rationale and Clinical Utility as it relates to Hormone Therapy:

- For many women, HT alleviates menopausal symptoms and provides protection in areas such as bone and cardiovascular function
- Cardiovascular risks tend to increase in post-menopause. For some women, the use of HT may further increase risk of myocardial infarction, stroke, and/or thromboembolism, as well as increase risk of breast cancer.
- The Women's Health Initiative (WHI) preliminary findings concluded that the risks associated with HT may outweigh the benefits.¹ Subsequent studies questioned this conclusion, particularly in the use of natural progesterone vs. synthetic progestins.²
- The risk/benefit ratio associated with HT varies between individuals. As a woman's response to HT will always be a function of both environmental and genetic influences, individualized risk assessment facilitates a more informed decision about treatment.

EstroGenomic™ Profile Markers:
ESTROGEN METABOLISM

CYP1A1 (Msp 1 and I462V polymorphisms)

CYP1B1 (V432L polymorphism)

COMT (V158M polymorphism)

GST (M1 and P1)

GSTM1 is a deletion allele (absent); enzyme activity is either present or absent.

GSTP1 polymorphisms: I105V and A114V

HYPERCOAGULATION RISK

GP3A (PIA1/PIA2)

PAI-1 (-675 4G/5G insertion/deletion polymorphism)

Factor 2 (G20210A polymorphism)

Factor V Leiden (Arg506Glu polymorphism)

CARDIOVASCULAR RISK

Apo E (Apo E2, E3, E4)

MTHFR (C677T and A1298C polymorphisms)

TNF- α (G308A polymorphism)

IL-6 (G174C polymorphism)

OSTEOPOROSIS RISK

VDR (BsmI RFLP)

COL1A1 (G2046T polymorphism)

TNF- α (G308A polymorphism)

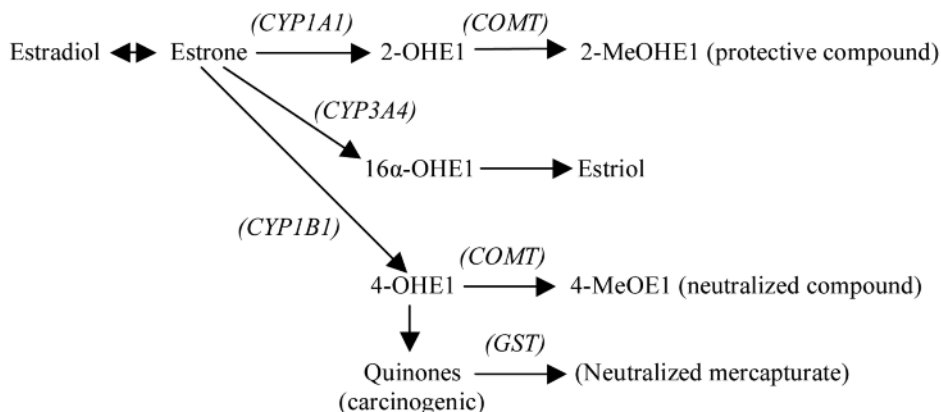
IL-6 (G174C polymorphism)

ESTROGEN METABOLISM:

Only about 5% of breast CA cases can be explained by rare, highly penetrant genes such as BRCA1 and BRCA2.³ First-degree relatives of breast cancer patients have a 2-fold increase in risk over the general population, most of which cannot be accounted for by BRCA1/2.⁴ It is likely that the interaction between environmental risk factors and the more prevalent but lower penetrance genes, especially those that influence estrogen metabolism, account for a much higher proportion of breast cancer cases.

Estrogens are metabolized to catechol estrogens (2- and 4-hydroxyestrogens) by Phase I enzymes such as CYP1A1 and CYP1B1, respectively. Phase II-conjugating enzymes such as COMT, GSTM1 and GSTP1 then catalyze the inactivation of these catechol estrogens. Polymorphisms in any of these genes may be a marker of altered estrogen metabolism and increased susceptibility to estrogen-related breast cancer.⁵

Estrogen Metabolism



CYP1A1 (Cytochrome P450 1A1)

(Polymorphisms: Msp 1, I462V)

CYP1A1 converts estrogens to 2-hydroxyestrogens, which are protective against breast cancer if methylated, but which may be carcinogenic if not.⁶ CYP1A1 also activates many environmental xenobiotics to pro-carcinogenic intermediates. A CYP1A1 polymorphism is associated with increased CYP1A1 enzyme activity. Whereas the MspI variant has been associated with both decreased and increased risk (in smokers) of breast cancer, the I462V variant has been linked in several studies with increased risk of cancer, especially in smokers and women exposed to PCBs.

CYP1B1 (Cytochrome P450 1B1)

(Polymorphism: V432L)

CYP1B1 converts estrogen to 4-hydroxyestrogen, a potent estrogen that may, in turn, be oxidized to carcinogenic compounds. A polymorphism is associated with increased enzyme activity, therefore increased production of these potentially harmful metabolites.⁷

COMT (Catechol-O-methyltransferase)

(Polymorphism: Val158Met)

COMT inactivates the carcinogenic compounds produced from 4-hydroxyestrogens^{8,9} and also methylates 2-hydroxyestrogens to compounds with anti-carcinogenic properties.¹⁰

A polymorphism in COMT is consistent with reduced COMT activity, hence greater cancer risk.^{11,12}

GST (M1 and P1) (Glutathione S-transferase)

(GSTM1 polymorphism is a deletion allele ("absent"); the GSTM1 genotype is identified as either present or absent).

(GSTP1 polymorphisms: Ile105Val, A114V).

GST enzymes detoxify the carcinogenic quinones and semi-quinones produced from 4-hydroxyestrogens, as well as many environmental xenobiotics.

Genotypes indicate either normal enzyme activity (if homozygous-negative or heterozygous), or absent (deleted) enzyme activity (if homozygous-positive).^{13,14} Several studies suggest increased breast cancer risk in women with GSTP1^{16,17} or GSTM1 polymorphisms.^{18,19}

Risk of postmenopausal breast cancer is further increased when both GST polymorphisms are present,²⁰ or when either SNP is combined with a homozygous positive SNP for COMT. Risk may increase as much as 3-4-fold when all three polymorphisms are present.²¹

HYPERCOAGULATION RISK

Fibrinolytic activity is decreased after menopause,²² which increases the risk of cardiovascular events. Although HT exerts some beneficial effects on the cardiovascular system, the use of oral HT has been linked to increased risk of clot formation, venous thromboembolism, pulmonary embolism, myocardial infarction, and/or stroke.

GP3A (Platelet glycoprotein IIIa)

(Polymorphism: PIA1/PIA2)

GP3A functions as a fibrinogen receptor on platelets that mediates thrombus formation.²³ A polymorphism results in a lower threshold for platelet activation, hence a greater tendency for platelets to aggregate. Platelet activation is an essential step in the formation of a clot. The GP3A SNP has been associated with a variety of vascular diseases,²⁴ especially in women.²⁵ Estrogen's inhibitory effect on platelet aggregation is highly dependent on the presence or absence of the SNP.²⁶

PAI-1 (Plasminogen activator inhibitor-1)

(Polymorphism: -675 4G/5G insertion/deletion)

PAI-1 is the primary inhibitor of plasminogen activation, contributing to fibrinolysis. Increased expression of PAI-1 is a significant risk factor for various cardiovascular conditions.^{27, 28} A polymorphism is associated with greater PAI-1 secretion, leading to reduced clot degradation.²⁹ Plasma PAI-1 increases post-menopausally;³⁰ estrogen therapy (oral more than transdermal)³¹ reduces PAI-1 in all genotypes;³² however 4G carriers may be particularly responsive.³³

Factor 2 (Prothrombin)

(Polymorphism: G20210A)

Prothrombin plays a key role in clot formation.³⁴ The polymorphism is associated with higher levels of prothrombin,³⁵ increased risk of venous thromboembolism (VTE),^{36, 37} early MI,^{38, 39} and stroke.⁴⁰ HT dramatically increases risk of VTE in a carrier of the polymorphism,⁴¹ but may protect against VTE in the wild type.⁴²

Factor V Leiden

(Polymorphism: Arg506Glu)

Factor V Leiden is a variant of factor V, one of the clotting proteins in the body. The polymorphism renders the factor V molecule resistant to normal inactivation by activated protein C (APC),⁴³ leading to a hypercoagulable state.⁴⁴ Heterozygotes and homozygotes are at 4-7 times and 50-100 times increased risk for venous thromboembolism, respectively.⁴⁵ HT dramatically increases risk of VTE in a carrier of the polymorphism,⁴⁶ but may protect against VTE in the wild type.⁴⁷

CARDIOVASCULAR RISK

Some risks for coronary artery disease are increased after menopause.⁴⁸ Oral HT has mixed effects on the cardiovascular system, conferring both benefit and risks. Genotype influences the effects of HT on cardiovascular function and risk.

Apo E (Apolipoprotein E)

(Apo E2, E3, E4)

The Apo E4 allele is generally associated with elevated total- and LDL-C levels, whereas the Apo E2 allele is associated with lower total- and LDL-C levels.⁴⁹ Apo E3's effect on cholesterol levels is intermediate between E2 and E4. Women with the Apo E4 allele have almost twice the risk of developing CHD.⁵⁰ HT improves the lipid profile in all ApoE genotypes, but particularly among Apo E4 carriers.^{51, 52} Although HDL-C is increased among Apo E2 users of oral HT, triglycerides are also more likely to be elevated.⁵³

MTHFR (Methylene tetrahydrofolate reductase)

(Polymorphisms: C677T, A1298T)

MTHFR is an enzyme that assists in the ultimate remethylation of homocysteine to methionine. Homozygotes are prone to elevations in homocysteine (Hcy), defective methylation,⁵⁴ and increased risk of various CV disorders.^{55, 56, 57, 58} Risk among heterozygotes is largely dependent upon folate status.⁵⁹ The influence of the SNP on Hcy is most pronounced in menopause, when Hcy levels tend to increase.^{60, 61} HT appears to reduce Hcy in all MTHFR genotypes.

TNF- α (Tumor necrosis factor- α)

(Polymorphism : G308A)

TNF- α has pro-atherogenic effects on blood vessel walls.⁶² TNF- α also induces IL-6 production, which stimulates the production of C-reactive protein (CRP), an independent risk factor for cardiovascular events.⁶³ The polymorphism also conveys increased risk for developing insulin resistance in obese individuals.⁶⁴ Homozygotes tend toward a higher BMI and waist/hip ratio and higher insulin and glucose levels compared with the wild type.⁶⁵ TNF- α levels increase as estrogen levels decline.²⁶ This trend is reversed with estrogen replacement (oral or transdermal).⁴⁵

IL-6 (Interleukin-6)

(Polymorphism : G174C)

Individuals carrying the variant allele may have a temporary but more dramatic response of IL-6 during the acute-phase response compared with the wild-type genotype. They also tend to have higher levels of CRP, an independent risk factor for cardiovascular disease.⁶⁶ On the other hand, the wild-type is associated with higher baseline levels of IL-6 and chronic inflammation.^{67, 68} An elevated baseline IL-6 level is considered an important predictor of cardiovascular risk among post-menopausal women.⁶⁹ IL-6 levels increase as estrogen levels decline in menopause.^{70, 71} Estrogen replacement tends to reduce IL-6⁷² and oppose the accumulation of visceral fat (producer of IL-6) in menopause.⁷³

OSTEOPOROSIS RISK

The risk of osteoporosis and fracture increases in early menopause, when the decline in estrogen results in accelerated bone loss. Estrogen replacement therapy prevents this acceleration, thus reducing the risk of osteoporosis.

VDR (Vitamin D receptor)

(Bsm1 RFLP)

The vitamin D receptor (VDR) mediates both the activation of vitamin D₃⁷⁴ and the actions of vitamin D₃, whose most important role is to maintain blood levels of calcium. Both effects help to spare the calcium that is stored in bones. The VDR polymorphism is associated with reduced calcium absorption,⁷⁵ reduced BMD,⁷⁶ and increased risk of fracture.⁷⁷ Homozygous-negative women have the most favorable bone response to HT and bisphosphonates,^{78, 79} but the least favorable response to raloxifene.⁸⁰

COL1A1 (Collagen 1alpha1)

(Polymorphism : G2046T)

Type 1 collagen is the major protein constituent in bone. A polymorphism in COL1A1 is associated with an increased rate of bone loss after menopause, and increased risk of osteoporosis and fracture, particularly in homozygotes.⁸¹ Because the polymorphism affects quality of bone as much as quantity, fracture risk may be increased in some women despite normal bone density.⁸² HT appears to nullify the adverse effect of the polymorphism on bone.⁸³

TNF- α (Tumor necrosis factor- α)

(Polymorphism : G308A)

The acceleration of bone loss in early menopause appears to be closely related to increased inflammatory cytokine activity.^{84, 85} TNF- α is a powerful stimulant of bone resorption.⁸⁶ Levels are increased in women with low estrogen levels. Estrogen replacement reverses this trend.⁸⁷ The polymorphism is associated with increased TNF- α production.⁸⁸ Osteoporotic women with the wild type genotype have greater BMD compared with women with the polymorphism.⁸⁹

IL-6 (Interleukin-6)

(Polymorphism : G174C)

Within the first ten years of menopause, IL-6 levels tend to increase and are the single most important predictor of bone loss at the hip, accounting for up to a third of the total variability of change in BMD.⁹⁰ The principal role of estrogens in bone metabolism is to inhibit IL-6 production in osteoblasts and bone marrow stromal cells.⁹¹ The wild type genotype (associated with higher baseline IL-6 levels)^{92, 93} is associated with greater bone resorption and lower BMD compared with the polymorphism.⁹⁴ Estrogen replacement tends to counter the increased production of IL-6 after menopause.⁹⁵

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