ESTROGEN METABOLISM & GENOMIC TESTING

The Impact on Breast Cancer in Women

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Women have a higher risk for breast cancer based on their cumulative life-time exposure to estrogen. In fact, it is an independent risk factor for breast cancer in women. Estrogen exposure can be from endogenous or exogenous sources, such as birth control pills, fertility treatments, hormone replacement therapy, bio-identical hormones, or in the treatment of various chronic diseases including polycystic ovary disease, endometriosis, vaginal bleeding or osteoporosis.

The dual role of estrogen, or more specifically estradiol, as a fertility hormone and a pro-carcinogenic molecule has received considerable attention in the research community in two areas. First, in trying to better understand the molecular action of the hormone and second, how to protect women from its carcinogenic effects.

Estradiol is a powerful hormone, responsible for many key functions. It is essential for the development of the female reproductive tract, regulating a woman's pubertal development and menstrual cycles. In conjunction with another hormone, progesterone, estradiol initiates secondary sex characteristics at the time of puberty, prepares the endometrium for implantation, and has multiple roles in various tissues including bone, brain, blood vessels, and liver.

On the other hand, estradiol has been associated with the development and progression of breast, ovarian and endometrial cancer. Estradiol affects target tissues in the breast by interacting with two nuclear receptors: estrogen receptor alpha (ER-alpha) and estrogen receptor beta (ER-beta). Estradiol preferentially binds with ER-alpha and once it does, the receptor complex modulates gene expression by binding to specific DNA sequences, increasing cell division, DNA replication and DNA damage. In most cases, cells respond to damaged DNA by initiating DNA repair. But, if the repair process is compromised by genetic mutations (e.g. BRCA1, BRCA2 genes), cellular processes are altered, resulting in cancer cell proliferation. To make this situation even worse, estradiol activates the proliferation and rapid growth of...
abnormal cells in the breast by modulating gene transcription and gene expression, leading to the most prevalent type of breast cancer: estrogen receptor positive or ER+.

**BREAST CANCER RATES ARE INCREASING**

Although the general perception is that all types of breast cancer are slowly declining in the US, National Cancer Institute reported that breast cancer rates will skyrocket by 2030. It is predicted that rate of breast cancer will grow from 283,000 cases in 2011 to 441,000 in 2030—a more than 50% increase. Even more troubling is the type of cancer that is expected to rise. The number of *in situ* tumors that are ER+ are projected to increase from 19% to 29%, and the proportion of new breast cancer cases in women age 70 to 84 is expected to increase from 24% to 35%, due mainly to the aging baby boom generation. The good news is that, compared to the other types of breast cancer, there are certainly more effective treatment options for ER+ breast cancer tumors. But it is also potentially the most preventable. Given the associated emotional, physical, financial and medical costs for women with breast cancer and their families, an ounce of prevention is worth a pound of cure.

**GENOMICS, ESTROGEN AND BREAST CANCER**

In terms of absolute serum levels and estrogenic activity, estradiol is the most potent estrogen in a female's body during her reproductive years and fortunately, there are enzymatic pathways responsible for its deactivation (detoxification) and removal from the body. Deactivation of estradiol includes biotransformation to less-reactive estrogens such as estrone, estriol, and 2-OH estrone. However, genes responsible for encoding the enzymes necessary to convert estradiol to the less active estrogen metabolites can undergo changes called single nucleotide polymorphisms (SNPs). These SNPs can alter gene expression and enzyme function, and can
compromise these biochemical processes, conferring an increased breast cancer risk. The more gene SNPs or variants within the estradiol detoxification pathway, the higher the breast cancer risk – particularly ER+. In post-menopausal women, breast cancer risk has been shown to be increased 13-fold when multiple gene SNPs occurred in the estrogen gene detoxification pathway. Gene SNPs were found to alter enzyme activity in three main ways: preferentially routing estrone to 4-OH estrone (a carcinogenic estrogen metabolite), reducing the ability to quench free radicals, and failing to methylate toxic estrogen metabolites.

Genoma International offers genomic testing designed to uncover these gene SNPs and provide evidence-based nutrigenomic action steps. Using this information, healthcare professionals can now recommend effective strategies to reduce the risk of breast cancer in pre-, peri- and postmenopausal women -- regardless of their endogenous level of estradiol or exogenous estradiol treatments. Psychologically, DNA-directed nutrigenomic strategies can give a woman piece of mind that she is doing everything to minimize her risk of breast cancer or prevent its recurrence. Several laboratories in the US provide physiological/biomarker testing to assess many of the nontoxic and toxic estrogen metabolites associated with the detoxification of estradiol. These tests can be used before and after a nutrigenomic intervention to determine the efficacy of the intervention, and guide adjustments to the nutrigenomic protocols when necessary throughout her lifetime.

CONCLUSION

It is important that every woman have a genomic test to determine how gene SNPs associated with her estrogen detoxification pathway are impacting her risk of breast cancer. Especially important are those women who have been diagnosed with ER+ breast cancer, have conditions associated with excess estrogen, as well as those who are considering oral contraceptives, traditional or bio-identical hormone replacement therapy, or those who are contemplating in-vitro fertilization treatments – for these women are at highest risk.
References

Estrogen as a Carcinogen


Gene Variants, Estrogen Metabolism and Breast Cancer Risk


**Nutrigenomic Interventions, Estrogen Metabolism and Breast Cancer Risk**


**Urinary Estrogen Metabolite Biomarkers and Breast Cancer Risk**
