Pia Sillanpää: Polymorphic low penetrance genes and breast cancer. The role of genes involved in metabolism of xenobiotics, estrogens and reactive oxygen species.

Various endogenous and exogenous factors have been reported to increase the risk of breast cancer. Many of those are related to prolonged lifetime exposure to estrogens. Furthermore, a positive family history of breast cancer and certain benign breast diseases are known to increase the risk of breast cancer. The role of lifestyle factors, such as use of alcohol and smoking has been an area of intensive study. Alcohol has been found to increase the risk of breast cancer, whereas the role of smoking has remained obscure.

A multitude of enzymes are involved in the metabolism of estrogens and xenobiotics including the carcinogens found in tobacco smoke. Many of the metabolic enzymes exhibit genetic polymorphisms that can lead to inter-individual differences in their abilities to modify hazardous substrates. Therefore, in presence of a given chemical exposure, one subgroup of women may be more susceptible to breast carcinogenesis, since they carry unfavourable forms of the polymorphic genes involved in the metabolism of the chemical.

In this work, polymorphic genes encoding for cytochrome P450 (CYP) 1A1 and 1B1, N-acetyl transferase 2 (NAT2), sulfotransferase 1A1 (SULT1A1), manganese superoxide dismutase (MnSOD) and vitamin D receptor (VDR) were investigated in relation to breast cancer susceptibility in a Finnish population. CYP1A1, CYP1B1 and SULT1A1 are involved in the metabolism of both estrogens and xenobiotics, whereas NAT2 is involved only in the latter. MnSOD is an antioxidant enzyme protecting cells from oxidative damage. VDR, in turn, mediates the effects of the active form of vitamin D (1,25(OH)2D3, calcitriol) on maintenance of calcium homeostasis and it has anti-proliferative effects in many cancer cells.

A 1.3-fold (95% CIs 1.01-1.73) increased risk of breast cancer was seen among women who carried the NAT2 slow acetylator genotype and a 1.5-fold (95% CI 1.1-2.0) risk was found in women with a MnSOD variant A allele containing genotypes compared to women with the NAT2 rapid acetylator genotype or to those with the MnSOD VV genotype, respectively. Instead, women with the VDR a allele containing genotypes were found to be at a decreased risk for breast cancer (OR 0.73; 95% CI 0.54-0.98) compared to women with the AA genotype. No significant overall associations were found between SULT1A1 or CYP genotypes and breast cancer risk, whereas a combination of the CYP1B1 432Val allele containing genotypes with the NAT2 slow acetylator genotypes posed a 1.5-fold (95% CI 1.03-2.24) increased risk. Moreover, NAT2 slow acetylator genotype was found to be confined to women with an advanced stage of breast cancer (stages III and IV).

Further evidence for the association of xenobiotic metabolising genes with breast cancer risk was found when active smoking was taken into account. Women who smoked less than 10 cigarettes/day and carried at least one CYP1B1 432Val variant allele, were at 3.1-fold (95% CI 1.32-7.12) risk of breast cancer compared to women who smoked the same amount but did not carry the variant allele. Furthermore, the risk was significantly increased with increasing number of the CYP1B1 432Val alleles (p for trend 0.005). In addition, women who smoked less than 5 pack-years and carried the NAT2 slow acetylator genotype were at a 2.6-fold (95% CI 1.01-6.48) increased risk of breast cancer compared to women who smoked the same amount but carried the NAT2 rapid acetylator genotype. Furthermore, the combination of the CYP1B1 432Val allele and the NAT2 slow acetylator genotype increased the risk of breast cancer by 2.5-fold (95% CI 1.11-5.45) among ever smokers. Instead, the MnSOD A allele was found to be a risk factor among postmenopausal long-term smokers (>15 years of smoking) (OR 5.1; 95% CI 1.4-18.4) or among postmenopausal women who had smoked more than 10 cigarettes/day (OR 5.5; 95% CI 1.3-23.4) compared to women who had similar smoking habits but carried the MnSOD V/V genotype.

Similarly, within subgroups of postmenopausal women who were using oral contraceptives, hormone replacement therapy or alcohol, women carrying the MnSOD A allele genotypes seemed
to be at increased risk of breast cancer compared to women with the MnSOD V/V genotype. A positive family history of breast cancer and high parity were shown to be inversely associated with breast cancer risk among women carrying the VDR ApaI allele or among premenopausal women carrying the SULT1A1*2 allele, respectively.