

**Polymorphisms in DNA double-strand break repair genes and breast cancer risk.**

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Enhanced chromosomal radiosensitivity (CR) has been observed in a significant number of breast cancer patients. Since ionising radiation induces double-strand breaks (DSB), polymorphisms in DSB repair genes could be involved in genetic predisposition to breast cancer. A family history of breast cancer is a well known risk factor for the disease. Other risk factors are also associated with breast cancer, such as early age of first menarche, nulliparity or late first childbirth, and late menopause. The principle culprit common for these risk factors is said to be the prolonged exposure to elevated levels of estrogens. As non homologous end-joining (NHEJ) is the major DSB repair pathway in mammalian cells, we investigated the association of 5 SNPs in 3 different NHEJ genes with breast cancer in a population-based case-control setting. The total patient population was composed of a selected group of patients with a family history of the disease and an unselected group. CR was previously studied in both patient groups. SNP analysis showed that the c.2099-2408G>A SNP (Ku80) has a significant odds ratio (OR) of 2.81 (95% confidence interval (CI): 1.30-6.05) for the heterozygous (He) and homozygous variant (HV) genotypes in the group of familial patients. The He+HV genotypes of the c.2099-2408G>A SNP (Ku80) also showed high and significant ORs in the group of radiosensitive, familial breast cancer patients (OR=4.62 ,95%CI: 1.28-16.74). For the c.-1310 C>G SNP (Ku70) a significant OR of 1.85 (95%CI: 1.01-3.41) was found for the He genotype in the unselected patient group. For the radiosensitive, unselected patients, increased, but non-significant ORs were observed. The c.-1310 C>G SNP (Ku70) SNP exhibits significant results in the unselected patient group only, indicating an influence of other, environmental factors besides genetic factors. As breast epithelium is exposed to endogenous oxidative stress through increased estrogen exposure, the possible effect of hormone exposure was examined in an enlarged, unselected patient population (OR enlarged population =1.68, 95%CI:1.09-2.60). The ORs of the c.-1310 C>G SNP (Ku70) SNP for patients with a longer estrogen exposure were high and significant (early menarche: OR=1.85, 95%CI:1.20-2.92; late menopause: OR=1.94, 95%CI:1.08-3.51) while the ORs for patients with a short hormone exposure were lower and non-significant. These results provide preliminary evidence that the variant allele of c.-1310C>G (Ku70) and c.2099-2408G>A (Ku80) are risk alleles for breast cancer as well as CR. Furthermore, the association of c.-1310C>G (Ku70) with breast cancer risk was stronger in women with a long estrogen exposure.