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Genetic Polymorphisms in DNA-Repair and Cell Cycle Control Genes as Biomarkers for the Development of Acute Side Effects of Radiotherapy in Breast Cancer Patients

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There is evidence that the variation in normal tissue reactions to radiotherapy may be partly determined by genetic factors. Both DNA repair and cell cycle control play an important role in the regeneration of the IR-induced damaged cells. Therefore, we evaluated the association of nine polymorphisms in the DNA repair genes (*XRCC1* Arg194Trp, Arg280His and Arg399Gln, *APE1* Asp148Glu, *XPD* Asp312Asn and Lys751Gln, *XRCC3* Thr241Met, *XRCC2* Arg188His and *NBS1* Glu185Gln) and three polymorphisms in cell cycle control genes (*TP53* Arg72Pro, *p53PIN* and *p21* Ser31Arg) with the risk of acute skin reactions following radiotherapy.

A prospective study of 446 female patients with breast cancer who received radiotherapy after breast-conserving surgery was conducted. The *XRCC3* Thr241Met polymorphism was determined by PCR-RFLP and the *p53*PIN3 polymorphism by standard PCR analysis. The other polymorphisms were identified using melting point analysis of sequence-specific hybridisation probes. The development of acute skin reactions (moist desquamation) associated with genetic polymorphisms was modelled in relation to the cumulative biologically effective radiation dose using Cox proportional hazards. The HRs and 95% CIs, adjusted by BMI, the variables hospital, photon beam energy for whole breast irradiation and boost irradiation, were quantified the association between genetic polymorphisms and acute skin toxicity after radiotherapy.

Overall, the development of acute toxicity, which presented in 77 patients, was not associated with the genetic variants studied. Risks were however differential by body mass index. Four genotypes *XRCC1* Arg399Gln, *APE1* Asp148Gln, *XPD* Lys751Gln and *TP53* Arg72Pro showed

marginally significant main effects individually in subgroup of normal weight patients (BMI ≤ 25.0). The results for *XRCC1 and TP53* were confirmed by haplotype analysis. When considering joint effects, we observed that, compared to homozygote carriers of the wild-type allele in both genes, the risk was most strongly reduced in carriers of both *APE1* 148Glu and *XRCC1* 399Gln alleles with normal weight (HR 0.19; 95% CI, 0.06-0.56) but not in those with overweight (HR 1.39; 95% CI, 0.56-3.45) (P for interaction = 0.009). Joint effects of the genotypes in DNA repair genes and *TP53* were also found among patients with normal weight. Furthermore, we assessed the combined effects of the variant alleles of *XRCC1* 399Gln, *APE1* 148Glu, *XPD* 751Gln and *TP53* 72Pro and demonstrated a strongly significant decreased risk of developing acute skin toxicity after radiotherapy with two or more of the variant alleles in women with normal weight.

In conclusion, the *XRCC1*-399Gln *APE1* 148Glu, *XPD* 751Gln and *TP53* 72Pro alleles may be protective against the development of acute side effects after radiotherapy in patients with normal weight. The genetic component of clinical radiation reactions should be considered as a polygenic trait. Larger studies based on multiple genetic markers are necessary to generate genetic profiles to predict normal tissue responses after radiotherapy.