Iron overload has been noticed as a feature of human breast cancer. Cellular iron uptake is regulated by the hemochromatosis and transferrin receptor system, mutations of which cause the iron storage disease hereditary hemochromatosis. To understand the role of hemochromatosis and transferrin receptor system mutations in breast cancer, we analyzed 19 sequence variations at HFE, TFR1, TFR2, and FPN1 and compared genotype frequencies between cases and controls in a German population. There were 688 breast cancer patients and 724 population-based and age-matched controls. For genotyping, we applied the Hemochromatosis Strip Assay and TaqMan allelic discrimination analyses. In addition to genotype frequencies, we established frequencies of compound genotypes. The frequencies of HFE at His63Asp, Ser65Cys, and Cys282Tyr, and of TFR1 at Ser142Gly minor alleles in this German population were 15.9%, 1.8%, 5.6%, and 46.0%, respectively. No rare variants at 15 more loci at HFE, TFR2, and FPN1 were observed in breast cancer patients. There were no significant differences of allele and genotype frequencies between cases and controls. Triple and quadruple compound genotypes at HFE_His63_Cys282-TFR1_Ser142Gly and HFE_H...
is63_Ser65_Cys282-TFR1_Ser142Gly showed a nonsignificant increase in cases. Although limited by low numbers, an increased prevalence of the HFE Tyr282 minor allele was observed in breast cancer cases with a high number of affected lymph nodes (P = 0.032). Our data suggest that variants of the hemochromatosis-transferrin receptor system have no direct effect on the incidence of breast cancer in Germany. Possible effects on tumor progression and prognosis remain elusive.