Limited relevance of the CHEK2 gene in hereditary breast cancer.

To establish the importance of CHEK2 mutations for familial breast cancer incidence in the German population, we have screened all 14 of the coding exons in 516 families negative for mutations in both the BRCA1 and BRCA2 genes. We found 12 distinct variants in 30 unrelated patients (5.81%), including 5 that are novel and an additional 4 found for the first time in breast cancer. These aberrations were evaluated in 500 healthy women aged over 50 years and in the case of the 2 exon 10 mutations, 1100delC and 1214del4bp, in 1315 randomized healthy controls. According to our results, a statistically significant association for the exon 10 mutations was observed (p = 0.006). The prevalence of the 1100delC mutation in the German population, however, is significantly lower than those reported for other Caucasian populations both in familial breast cancer patients (1.6%) and controls (0.5%), and shows independent segregation with breast cancer in 2 of 4 families analyzed. The remaining 10 variants were more abundant in patients (21) compared to the controls (12) although the difference was not statistically significant. Interestingly, we found no increased breast cancer risk associated with the splice site mutation IVS2+1G-->A or the most common missense mutation I157T,
which account for more than half (12/21) of the variants observed in patients. The low prevalence and penetrance of the exon 10 deletion mutations together with no, or an uncertain elevation in risk for other CHEK2 mutations suggests a limited relevance for CHEK2 mutations in familial breast cancer. Further evaluation of the unique variants observed in breast cancer is required to determine if they may play a role in a polygenic model of familial breast cancer. Nevertheless, it seems premature to include CHEK2 screening in genetic testing.